Tissue Detoxification and Health Supplements and Methods of Making and Using Them

FIELD OF THE INVENTION

This invention relates to preparations and formulations comprising beneficial phytochemical ingredients that are serviceable as health supplements for the body, including a human body, and particularly for tissues susceptible to cancer, including, e.g. prostate tissue and breast tissue, for example, female breast tissue. These preparations and formulations of the invention can be used to maintain the health of a tissue or organ, e.g., breast tissue, act as a prophylactic to disease or condition, or ameliorate a disease state or condition.

This invention also relates to preparations comprising chelating agents that are effective (serviceable) for heavy metal detoxification of humans and animals. These preparation can, in non-limiting fashion, be administrated orally, parenterally, or transdermally (e.g., by topical spray, lotion or cream). In non-limiting exemplifications, this invention provides novel preparations of chelating agents encapsulated in micelles or liposomes comprising the triple combination of 1) micelles or liposomes comprising alpha lipoic acid and 2) micelles or liposomes comprising EDTA (ethylene-diaminetetraacetic acid) or other chelators; and furthermore, in different embodiments, 3) magnesium chloride is optionally an additional ingredient in these novel preparations. These preparations and formulations of the invention can be used to maintain the health of a tissue or organ, act as a prophylactic to a disease or condition, or ameliorate a disease state or condition.

This invention also relates to combinations, such as kits, comprising both a preparation of chelating agents, and a preparation of phytochemical ingredients.

BACKGROUND OF THE INVENTION

Tissue Health

The ability to maintain the health of and to achieve the detoxification of tissues can be aided by many dietary supplements. However, in disease states, e.g. cancer, the cause of the disease may become refractory or resistant to a single-pronged approach to health and detoxification. Thus, this invention provides multi-pronged approaches that make advantageous use of novel combinations of ingredients that provide beneficial effects.

Toxicity and poisoning.

Heavy metal poisoning is a serious medical problem that is receiving even more emphasis in recent years as the ability to detect toxic metals, as well as the ability to understand the detrimental affects associated therewith, have progressed compared to the past. Furthermore, it is known that toxic heavy metals such as lead, arsenic and mercury may very easily enter the body as a consequence of, to name a few examples, accumulated exposure, accidents, environmental pollution, and oral consumption (e.g. food or paint). For example, exposures to lead and mercury are wide-spread and well documented. Poisoning from excessive concentrations of substances that would other wise be beneficial at lower concentrations is also known; e.g. iron poisoning has been reported. Arsenic can get into the body, e.g. as a result of industrial pollution. Also of concern are radioactive toxic heavy metals that pose an additional problem due to their radioactivity. These must be eliminated as quickly as possible, because the ionizing radiations of the radioactive metals pose the risk of tumor induction from their radioactive ionization, including by altering DNA. Toxic heavy metals are also known to concentrate in various organs of the body. Plutonium, for example, usually deposits in the liver, and it is known that as much as 30 to 60% or more of an administered amount of plutonium will oftentimes deposit in the liver. The toxic heavy metal, plutonium in this example, remains in the organ and is only very slowly removed, thereby increasing the potential for tumors.

Summary of challenges with traditional treatments.

1) Intravenous (I.V.) chelation is expensive, time-consuming, and has poor patient compliance. 2) Traditional oral chelation therapies are cheaper, but they are relatively ineffective at their intended purposes, and, at higher doses, are accompanied by side effects. For example, the oral administration of chelating agents by traditional approaches is problematic not only because their poor absorption and bioavailability prevents them from reaching the bodily stores of toxins and heavy metals, but furthermore they can chelate beneficial substances in the digestive tract. 3) Using traditional therapies, neither parenterally (e.g. by I.V.) nor orally administered chelating agents are able to enter the intracellular compartments where toxins and heavy metals are also present. Traditional therapies for the parenteral administration of chelating agents using physiologically compatible aqueous solutions (e.g. saline, Ringer's solution, etc.), fail to cause absorption of lipid soluble agents, because of inherent solubility problems.

1) Challenges with I.V. chelation therapies.

Heavy metal detoxification can be accomplished using I.V. chelation with ingredients such as EDTA; this approach has been documented to be effective and safe, and EDTA was approved by the FDA for this use in the 1950's. The ability of I.V. chelation therapy to diminish and even dissolve arterial plaques has also been reported. However, I.V. chelation is very expensive and time-consuming, typically requiring a patient make a series of 20 to 50 visits to a physician's office or hospital (at least 30 visits are typically required), with each visit often taking from 3-4 hours, during which time the patient is typically seated, and costing up to $100 or more per visit.

2) Challenges with orally administered chelation therapies.

Oral chelation products are commercially available, and they are marketed as much less expensive alternatives to I.V. chelation therapies. However, EDTA is very poorly absorbed when administered by mouth; and the general consensus is that typically only about five percent or less is absorbed. Although even that small amount does remove lead from the body, it also been reported to increases the absorption of lead.

Other serious potential problems have been reported as well. For example, it has been reported that the unabsorbed 95 percent of EDTA that remains within the digestive tract, mixes with undigested food and nutrients while passing on out of the body in stool. This unabsorbed EDTA tightly binds to and blocks absorption of many essential nutritional trace elements as it passes through, thereby potentially blocking the uptake of important nutrients such as zinc, manganese, chromium, vanadium, copper, chromium, molybdenum and other essential nutrients, causing deficiencies.

When a chelator such as EDTA enters the body, either by mouth or intravenously, it could possibly remove 10 to 20 times more of the essential nutritional trace elements (such as zinc and manganese) than it does the undesired heavy metals or toxins that are deleterious. When given intravenously, thus bypassing any absorption problems, a full therapeutic treatment of EDTA can be completed with 20 to 50 daily doses. The replenishment of the lost essential trace elements by dietary supplementation can then take place during the remaining 315+ days of the year after the treatment, when the exogenously administered chelating agent(s) such as EDTA have been excreted or eliminated, and are not present to interfere. Because such a small amount is absorbed by mouth, oral EDTA is often given every day, but for up to 20 times or more as long, to accumulate what is alleged to be an effective dose, and there is no interim opportunity to

replenish the essential nutrients that are being continuously blocked and depleted during the chelation therapy.

Thus, the daily administration of chelating agents such as EDTA by mouth may cause progressive deficiencies of zinc, manganese and other essential trace nutrients, which are an essential part of the body's antioxidant defenses. For example, the activity of superoxide dismutase (SOD), a very important intracellular antioxidant, depends on zinc and manganese. By inactivating antioxidant enzymes, the daily intake of chelation agents by mouth may actually worsen the condition of the patients being treated.

Intravenous chelation therapy has been reported to stimulate the release of parathyroid hormone (parathormone) in a pulsatile manner, but orally administered chelation therapies, such as with EDTA, have not. Thus, if that mechanism of action is important to achieve the intended benefit, oral EDTA cannot achieve the goal.

Attempts have been reported to increase the amount of chelating agents that are used in an oral chelation therapy to match the levels that can be achieved when they are administered intravenously. However, there are many side effects that prevent this approach from being used.

3) Challenges with both oral and I.V. chelation therapies.

The use of chelating agents for the removal of toxic heavy metals is based on their ability to form stable, nonionic, soluble and readily excretable complexes with the metal molecules in the tissues. They have proven valuable because they, in themselves, have a very low toxicity, are able to form soluble, excretable metal chelates within a body, and resist degradation by cell metabolites. However, the serious limitation for the use of chelating agents is that, when introduced into a body, they exist as hydrated anions in the blood plasma. These anions are unable to penetrate cellular membranes. Therefore, only extracellularly deposited toxic metals can be complexed by the chelating agents and removed from the body, whereas intracellularly deposited metals are not complexed by the chelating agent and therefore are not readily removed. Attempts have been made in the past to increase the penetration of chelating agents through cellular membranes such as by the esterification of polyaminopolycarboxylic acids, but these efforts have met with limited success because of the insolubility and toxicity of the esterified compounds.

Thus, chelators such as EDTA typically remain extracellularly or outside of cells. By way of illustration, orally administered EDTA reaches only very low concentrations outside cell surfaces in the body and for brief periods of time, while intravenous infusions result in much higher levels, and can be maintained for several hours. However,

intravenously administered EDTA can only chelate unwanted metals and toxins, if, e.g. they travel out of cell walls by diffusion. In contrast, this is not believed to occur to a significant extent – if at all – with chelators such as EDTA when taken by mouth. In sum, neither traditional approach achieves significant intracellular levels of chelating agents, and is thus unable to readily exert its actions intracellularly.

The preparations of the present invention comprise antioxidants that have effects that may be additive or synergistic to the effects of chelators such as EDTA; however, these antioxidants may be lipophilic. Because many parenterally suitable fluids such as saline, dextran, blood, stabilized hemoglobin solutions, etc., are all aqueous solutions, a problem with therapies based on lipid soluble antioxidants, such as alpha-lipoic acid, is the poor water solubility of these ingredients. The solubility may be enhanced by adding benzyl alcohol or DMSO, but such solvents introduce additional side effects.

Previous methods of delivering lipophilic antioxidants that involved solubilizing the antioxidant in solvents such as benzyl alcohol, DMSO, or other chemicals not only have the potential to introduce new toxicities, e.g. they may exacerbate microvascular injury, but the presence of these solvents confuses the interpretation of any protocol designed to evaluate antioxidant effects.

SUMMARY OF THE INVENTION

The invention provides preparations comprising encapsulated chelating agents comprising at least one member of a first group, at least one member of a second group and at least one member of a third group, wherein members of the first group are selected from the group consisting of R-(+)-alpha-lipoic acid, S-(-)-alpha-lipoic acid, R/S-alpha-lipoic acid, R/S-gamma-lipoic acid, isomers of alpha lipoic acid, dihydrolipoic acid or DHLA, animal and vegetable oils, hydrocarbon oils, ester oils, silicone oils, higher fatty acids, higher alcohols, sun-screening agents, vitamins, and ferulic acid; members of the second group comprises at least one chelating group; and members of the third group are selected from the group consisting of lecithin, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, dilinoleylphosphatidylcholine, lysolipids, dipalmitoyl-phosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, fatty acids, palmitic acid, stearic acid, oleic acid, linolenic acid, linoleic acid, glycosphingolipids, glucolipids, glycolipids, sulphatides, lipids bearing sulfonated mono-, di-, oligo- or

polysaccharides, lipids with ether and ester-linked fatty acids, triglycerides, lipoproteins, cholesterol, a lipid and a polymerized lipid, wherein at least about 1% of members from the first, second or third group in the preparation are encapsulated in a microsphere or a liposome, and the microsphere or liposome comprises a member of the third group. In one aspect of the preparation one or more members of the first group, one or more members of the second group, and one or more members of the third group are admixed to generate a microsphere or a liposome.

The invention provides preparations comprising encapsulated bioavailable chelating agents comprising at least one member of a first group, at least one member of a second group and at least one member of a third group, wherein members of the first group are selected from the group consisting of R-(+)-alpha-lipoic acid, S-(-)-alpha-lipoic acid, R/S-alpha-lipoic acid, R/S-gamma-lipoic acid, other isomers of alpha lipoic acid, dihydrolipoic acid or DHLA, animal and vegetable oils, hydrocarbon oils, ester oils, silicone oils, higher fatty acids, higher alcohols, sun-screening agents, vitamins, and ferulic acid, wherein at least about 1% of the members of the first group in the preparation are encapsulated in a microsphere or a liposome; members of the second group are selected from the group consisting of EDTA (ethylene-diaminetetraacetic acid), ethyleneglycol-bis[beta-aminoethyl ether]-N,N'-tetra-acetic acid (EGTA), diethylenetriamine-pentaacetic acid (DTPA), triethylenetetraaminehexaacetic acid (TTHA), N-hydroxyethylenediaminehexaacetic-acid (HEDHA), 1,4,7-triazacyclononane-N,N',N"-triacetic acid (NOTA), 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA), N'-hydroxy-ethylenediamine-N,N,N'-triacetic acid (HEDTA), other polyaminopolycarboxylic acids, iminodiacetic acid (IDA), cyclam, penicillamine, dimercaptosuccinic acid, tartrate, thiomalic acid, crown ethers, nitrilotriacetatic acid (NTA), 3,6-dioxaoctanedithioamide, 3,6-dioxaoctanediamide, salicyladoximine, dithio-oxamide, 8-hydroxyquinoline, cupferron, 2,2'-thiobis(ethyl acetoacetate), 2,2'-dipyridyl, and derivatives thereof, wherein at least about 1% of the members of the second group in the preparation are encapsulated in a microsphere or a liposome; and members of the third group are selected from the group consisting of lecithin, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, dilinoleylphosphatidylcholine, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, fatty acids, palmitic acid, stearic acid, oleic acid, linolenic acid,

linoleic acid, glycosphingolipids, glucolipids, glycolipids, sulphatides, lipids bearing sulfonated mono-, di-, oligo- or polysaccharides, lipids with ether and ester-linked fatty acids, triglycerides, lipoproteins, cholesterol, a lipid and a polymerized lipid, wherein at least about 1% of the members of the third group in the preparation are encapsulated in a microspheres or a liposome, and the microsphere or liposome comprises a member of the third group. In alternative aspects of the preparation, at least about 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24% or 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48% or 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%, or more of the one or more members from the first, second or third group in the preparation are encapsulated in a microsphere or a liposome.

The invention provides kits or formulations comprising two preparations, a first preparation and a second preparation, wherein said first preparation comprises a phospholipid, a chelating agent, magnesium chloride, and alpha lipoic acid; and the second preparation comprises diindolemethane, grape extract or grape skin extract or wine extract, calcium D-glucarate, medium chain triglycerides or a phospholipid or a combination thereof. The grape extract or grape skin extract or wine extract can be a red grape extract, a red grape skin extract or a red wine extract. The chelating agent comprises EDTA (ethylene-diaminetetraacetic acid), diethylenetriamine-pentaacetic acid (DTPA), ethyleneglycol-bis[beta-aminoethyl ether]-N,N'-tetra-acetic acid (EGTA), triethylenetetraaminehexaacetic acid (TTHA), N-hydroxyethylenediaminehexaacetic-acid (HEDHA), 1,4,7-triazacyclononane-N,N',N"-triacetic acid (NOTA), 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA), N'-hydroxy-ethylenediamine-N,N,N'-triacetic acid (HEDTA), other polyaminopolycarboxylic acids, iminodiacetic acid (IDA), cyclam, penicillamine, dimercaptosuccinic acid, tartrate, thiomalic acid, crown ethers, nitrilotriacetatic acid (NTA), 3,6-dioxaoctanedithioamide, 3,6-dioxaoctanediamide, salicyladoximine, dithio-oxamide, 8-hydroxyquinoline, cupferron, 2,2'-thiobis(ethyl acetoacetate), 2,2'-dipyridyl or derivatives thereof.

The invention provides preparations comprising diindolemethane, grape extract or grape skin extract or wine extract, calcium D-glucarate, a medium chain triglyceride, a phospholipid, and at least one vitamin B9 molecule. The grape extract or grape skin

extract or wine extract can be a red grape extract, a red grape skin extract or a red wine extract. The at least one vitamin B9 molecule can be folate, folic acid and/or folinic acid. In one aspect, the vitamin B9 molecule comprises folic acid and folinic acid.

The invention provides kits or formulations comprising two preparations, a first preparation and a second preparation, wherein said first preparation comprises a plant indole, indole-3-carbinol (I3C) or its dimer 3,3'-diindolylmethane (DIM), grape extract or grape skin extract or wine extract, calcium D-glucarate, medium chain triglycerides, a phospholipid, and at least one vitamin B9 molecule; and the second preparation comprises a phospholipid, a chelating agent, magnesium chloride and alpha lipoic acid. The chelating agent can comprise EDTA (ethylene-diaminetetraacetic acid), diethylenetriamine-pentaacetic acid (DTPA), ethyleneglycol-bis[beta-aminoethyl ether]-N,N'-tetra-acetic acid (EGTA), triethylenetetraaminehexaacetic acid (TTHA), N-hydroxyethylenediaminehexaacetic-acid (HEDHA), 1,4,7-triazacyclononane-N,N',N''-triacetic acid (NOTA), 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA), N'-hydroxy-ethylenediamine-N,N,N'-triacetic acid (HEDTA), other polyaminopolycarboxylic acids, iminodiacetic acid (IDA), cyclam, penicillamine, dimercaptosuccinic acid, tartrate, thiomalic acid, crown ethers, nitrilotriacetatic acid (NTA), 3,6-dioxaoctanedithioamide, 3,6-dioxaoctanediamide, salicyladoximine, dithio-oxamide, 8-hydroxyquinoline, cupferron, 2,2'-thiobis(ethyl acetoacetate), 2,2'-dipyridyl and/or derivatives thereof. The at least one vitamin B9 molecule can be a folate, a folic acid and/or a folinic acid. In one aspect, the vitamin B9 molecule comprises folic acid and folinic acid.

The invention provides methods for detoxification of an animal comprising administering an effective amount of the preparation of the invention. The invention provides methods for detoxification of an animal comprising administering an effective amount of the formulation of the invention. The invention provides methods for detoxification of an animal comprising administering an effective amount of the preparation of the invention. The detoxification can comprise heavy metal detoxification, wherein the metal can be arsenic, lead, cadmium or mercury. In one aspect of a method of the invention, the animal is a human.

The invention provides methods wherein formulation or preparation is administered by inoculation, infusion or injection, topical application or by absorption through epithelial or mucocutaneous linings.

The invention provides liquids comprising the preparation of the invention, or formulation of the invention. The invention provides capsules, sprays, powders, lotions, tablets or pills comprising a preparation of the invention or formulation of the invention.

The invention provides foods or food supplements comprising a preparation of the invention or a formulation of the invention. The food or food supplement can comprise a flavored bar, a power bar, a diet bar, an energy bar or a nutritional bar.

The invention provides methods for maintaining the health of a tissue comprising administering an effective amount of a preparation of the invention or a formulation of the invention. The tissue can be a breast tissue or a prostate tissue. The invention provides methods for ameliorating a disease or condition in an individual comprising administering an effective amount of a preparation of the invention or a formulation of the invention. The disease or condition can affect breast tissue or prostate tissue.

The invention provides preparations or formulations wherein at least a fraction of the microsphere or liposome further comprises a gas comprising a nitrogen gas, oxygen gas, atmospheric air, gaseous mixtures containing nitrogen gas, gaseous mixtures containing oxygen gas, or a combination thereof. The invention provides preparations or formulations of the invention wherein the microsphere or liposome is homogeneous in size or in content, or, heterogeneous in size or in content.

The invention provides preparations or formulations comprising encapsulated chelating agents comprising at least one member of a first group, at least one member of a second group and at least one member of a third group, wherein members of the first group comprise at least one hydrophobic antioxidant; members of the second group comprises at least one chelating group; and members of the third group comprise at least on member selected from the group consisting of lecithin, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, dilinoleylphosphatidylcholine, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, fatty acids, palmitic acid, stearic acid, oleic acid, linolenic acid, linoleic acid, glycosphingolipids, glucolipids, glycolipids, sulphatides, lipids bearing sulfonated mono-, di-, oligo- or polysaccharides, lipids with ether and ester-linked fatty acids, triglycerides, lipoproteins, cholesterol, a lipid, a polymerized lipid and equivalent compounds, wherein at least about 1% of members from the first, second or third group in the preparation are encapsulated in a microsphere or a liposome.

The invention provides preparations or formulations comprising at least one member of a first group and at least one member of a second group, wherein the member of the first group comprises a plant indole, and the member of the second group in this or any preparation or formulation of the invention can comprise a plant flavonoid, a polyphenol, a stilbene, a 3,5,4′-trihydroxy stilbene, a resveratrol, a piceatannol, a grape extract, a grape skin extract or a wine extract, or an equivalent compound.

The invention provides preparations or formulations comprising at least one member of a first group and at least one member of a second group, wherein the member of the first group comprises a plant indole, and the member of the second group comprises a D-glucaric acid, a salt of a D-glucaric acid, a potassium hydrogen D-glucarate (PHG), a derivatized D-glucaric acid, a D-glucaro-l,4-lactone, a 1,4-GL, 2-keto-3-deoxy-D-glucarate, a 4-deoxy-5-keto-D-glucarate, or an equivalent compound.

The invention provides preparations or formulations comprising at least one member of a first group and at least one member of a second group, wherein the member of the first group comprises a plant indole, and the member of the second group comprises a medium chain triglyceride (MCT). The at least half of the content of the preparation or formulation in this or any preparation or formulation of the invention can comprise at least 80% of MCTs having a length of between C_5 and C_{11} . The MCT can be derived from coconut oil, palm kernel oil, camphor tree drupes, butter or a combination thereof. The MCT can comprise a lauric oil, or glycerol esters of caprylic acid, octanoic acid, capric acid or decanoic acid.

The invention provides preparations or formulations comprising at least one member of a first group and at least one member of a second group, wherein the member of the first group comprises a plant indole, and the member of the second group comprises lecithin, phophatidylcholine, phosphatidylserine, phosphatidylethanolamine, dilinoleylphosphatidylcholine, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, fatty acids, palmitic acid, stearic acid, oleic acid, linolenic acid, linoleic acid, glycosphingolipids, glucolipids, glycolipids, sulphatides, lipids bearing sulfonated mono-, di-, oligo- or polysaccharides, lipids with ether and ester-linked fatty acids, triglycerides, high density lipoprotein, low density lipoprotein, cholesterol, or other lipids or polymerized lipids or derivatives thereof. The

plant indole can comprise an indole-3-carbinol (I3C) or its dimer 3,3'-diindolylmethane (DIM), grape extract or grape skin extract or wine extract.

The invention provides preparations or formulations comprising at least one member of a first group and at least one member of a second group, wherein the member of the first group comprises a medium chain triglyceride (MCT), and the member of the second group comprises a D-glucaric acid, a salt of a D-glucaric acid, a potassium hydrogen D-glucarate (PHG), a derivatized D-glucaric acid, a D-glucaro-1,4-lactone, a 1,4-GL, 2-keto-3-deoxy-D-glucarate, a 4-deoxy-5-keto-D-glucarate, or an equivalent compound.

The invention provides preparations or formulations for oral administration comprising a chelating agent and a phospholipid, wherein the chelating agent and phospholipid are encapsulated in a microsphere or liposome comprising a compound selected from the group consisting of lecithin, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, dilinoleylphosphatidylcholine, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, fatty acids, palmitic acid, stearic acid, oleic acid, linolenic acid, linoleic acid, glycosphingolipids, glucolipids, glycolipids, sulphatides, lipids bearing sulfonated mono-, di-, oligo- or polysaccharides, lipids with ether and ester-linked fatty acids, triglycerides, lipoproteins, cholesterol, a lipid, a polymerized lipid and a derivatized lipid. The invention provides preparations or formulations wherein the chelating agent comprises disodium EDTA (ethylene-diaminetetraacetic acid), diethylenetriamine-pentaacetic acid (DTPA), ethyleneglycol-bis[beta-aminoethyl ether]-N,N'-tetra-acetic acid (EGTA), triethylenetetraaminehexaacetic acid (TTHA), N-hydroxyethylenediaminehexaacetic-acid (HEDHA), 1,4,7-triazacyclononane-N,N',N''-triacetic acid (NOTA), 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA), N'-hydroxy-ethylenediamine-N,N,N'-triacetic acid (HEDTA), other polyaminopolycarboxylic acids, iminodiacetic acid (IDA), cyclam, penicillamine, dimercaptosuccinic acid, tartrate, thiomalic acid, crown ethers, nitrilotriacetatic acid (NTA), 3,6-dioxaoctanedithioamide, 3,6-dioxaoctanediamide, salicyladoximine, dithio-oxamide, 8-hydroxyquinoline, cupferron, 2,2'-thiobis(ethyl acetoacetate), 2,2'-dipyridyl or derivatives thereof. The phospholipid can comprise alpha lipoic acid. The preparation can comprise disodium EDTA, phospholipid, magnesium chloride and alpha lipoic acid.

The preparation can comprise about 1 gm of disodium EDTA, about 30 gm of phospholipid, about 150 mg of magnesium chloride and about 100 mg of alpha lipoic acid.

The invention provides preparations formulated for oral administration, spraying, applying topically to a mucous membrane, inhaling, injecting or applying by using a patch or an implant, comprising indole-3-carbinol (I3C) or its dimer 3,3'-diindolylmethane (DIM), calcium D-glucarate and a red wine extract or grape extract or grape skin extract, wherein the indole-3-carbinol (I3C) or its dimer 3,3'-diindolylmethane (DIM), calcium D-glucarate and red wine extract are encapsulated in a microsphere or liposome comprising a compound selected from the group consisting of lecithin, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, dilinoleylphosphatidylcholine, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, fatty acids, palmitic acid, stearic acid, oleic acid, linolenic acid, linoleic acid, glycosphingolipids, glucolipids, glycolipids, sulphatides, lipids bearing sulfonated mono-, di-, oligo- or polysaccharides, lipids with ether and ester-linked fatty acids, triglycerides, lipoproteins, cholesterol, a lipid, a polymerized lipid and a derivatized lipid. The invention provides kits comprising these formulations, and in one aspect, the kit comprising instructions on using the formulation.

In one aspect, the preparation further comprises a medium chain triglyceride. The preparation can comprise calcium, diindolylmethane, red wine extract, calcium D-glucarate, medium chain triglyceride and lecithin. The preparation can comprises about 24 mg calcium, about 100 mg diindolylmethane, about 200 mg red wine extract, about 200 mg calcium D-glucarate, about 45 mg medium chain triglyceride and about 45 mg lecithin.

The invention provides preparations or formulations comprising at least one member of a first group and at least one member of a second group, wherein the member of the first group comprises a plant indole, and the member of the second group comprises a fat soluble vitamin or equivalent compound. The fat soluble vitamin or equivalent compound can comprise vitamin A, D, E or K, retinol, retinol derivatives, retinoic acid, carotenoids, lycopene, lutein, 1,25-dihydroxyvitamin D, calciferol, calcipotriol, cholecalciferol, ergocalciferol (vitamin D2), irradiated ergocalciferol, alpha tocopherol, tocopherol, tocopheryl acetate, tocopheryl succinate, phylloquinones, menaquinones, menadione or menatetrenone (vitamin K2).

The invention provides preparations or formulations comprising at least one member of a first group and at least one member of a second group, wherein the member of the first group comprises a plant indole, and the member of the second group comprises a lycopene, carotenoid, carotenes, xanthophyll, alpha-carotene, beta-carotene, lutein, cyptoxanthin, zeaxanthin and/or a plant-derived lycopene. The plant-derived lycopene in this or any preparation or formulation of the invention can comprise a blueberry-derived or a tomato-derived lycopene.

The invention provides preparations or formulations comprising at least one member of a first group and at least one member of a second group, wherein the member of the first group comprises a medium chain triglyceride (MCT), and the member of the second group comprises a fat soluble vitamin or equivalent compound. The fat soluble vitamin or equivalent compound in this or any preparation or formulation of the invention can comprise vitamin A, D, E or K, retinol, retinol derivatives, retinoic acid, carotenoids, lycopene, lutein, 1,25-dihydroxyvitamin D, calciferol, calcipotriol, cholecalciferol, ergocalciferol (vitamin D2), irradiated ergocalciferol, alpha tocopherol, tocopherol, tocopheryl acetate, tocopheryl succinate, phylloquinones, menaquinones, menadione or menatetrenone (vitamin K2).

The present invention provides methods for transferring at least two ingredients, comprising an antioxidant and a chelating agent, across a cellular membrane. Another object of the present invention is to provide a means for introducing at least two ingredients, comprising an antioxidant and a chelating agent, into the interior of a cell.

The invention provides methods for introducing at least two ingredients, comprising an antioxidant and a chelating agent, into the interior of a cell of a living organism by introducing the at least two ingredients to the organism and carrying it to the cell in the blood stream. In one aspect, the at least two ingredients are introduced by oral administration. Another object of the present invention is to provide a method for the removal of intracellularly deposited toxic heavy metals.

In one aspect, the present invention provides a therapy method for toxic heavy metal poisoning whereby both intracellularly deposited toxic heavy metals as well as extracellularly deposited toxic heavy metals can be removed from the body. In separate aspect, said body is a human body or an animal body (e.g. a pet or other raised animal, e.g., a farm or zoo animal).

In separate embodiments, this invention provides different products that comprise (contain at least) all the combinations and permutations of ingredients selected from

members of Group 1 (e.g. in Table 3), members of Group 2 (e.g. in Table 3), members of Group 3 (e.g. in Table 3), members of Group 4 (e.g. in Table 3), members of Group 5 (e.g. in Table 3), and members of Group 6 (e.g. in Table 3). The following embodiments illustrate these combinations and permutations.

In one embodiment, the invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM, or diindolylmethane); and b) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); and b) one or more members selected from Group 3 (e.g. calcium D-glucarate).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); and b) one or more members selected from Group 4 (e.g. medium chain triglycerides).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); and b) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); and b) one or more members selected from Group 6 (e.g. lycopenes and carotenoids).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); and b) one or more members selected from Group 3 (e.g. calcium D-glutarate).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); and b) one or more members selected from Group 4 (e.g. medium chain triglycerides).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); and b) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 3 (e.g. calcium D-glutarate); and b) one or more members selected from Group 4 (e.g. medium chain triglycerides).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 3 (e.g. calcium D-glutarate); and b) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); and b) one or more members selected from Group 6 (e.g. lycopenes and carotenoids).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 4 (e.g. medium chain triglycerides); and b) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 3 (e.g. calcium D-glutarate); and b) one or more members selected from Group 6 (e.g. lycopenes and carotenoids).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); and c) one or more members selected from Group 3 (e.g. calcium D-glucarate).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); and c) one or more members selected from Group 4 (e.g. medium chain triglycerides).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); and c) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 4 (e.g. medium chain triglycerides); and b) one or more members selected from Group 6 (e.g. lycopenes and carotenoids).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 3 (e.g. calcium D-glucarate); and c) one or more members selected from Group 4 (e.g. medium chain triglycerides).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 3 (e.g. calcium D-glucarate); and c) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); and c) one or more members selected from Group 6 (e.g. lycopenes and carotenoids).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 4 (e.g. medium chain triglycerides); and c) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 3 (e.g. calcium D-glucarate); and c) one or more members selected from Group 6 (e.g. lycopenes and carotenoids).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); b) one or more members selected from Group 3 (e.g. calcium D-glucarate); and c) one or more members selected from Group 4 (e.g. medium chain triglycerides).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); b) one or more members selected from Group 3 (e.g. calcium D-glucarate); and c) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 4 (e.g. medium chain triglycerides); and c) one or more members selected from Group 6 (e.g. lycopenes and carotenoids).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); b) one or more members selected from Group 4 (e.g. medium chain triglycerides); and c) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); b) one or more members selected from Group 3 (e.g. calcium D-glucarate); and c) one or more members selected from Group 6 (e.g. lycopenes and carotenoids).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 3 (e.g. calcium D-glucarate); b) one or more members selected from Group 4 (e.g. medium chain triglycerides); and c) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); b) one or more members selected from Group 4 (e.g. medium chain triglycerides); and c) one or more members selected from Group 6 (e.g. lycopenes and carotenoids).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); c) one or more members selected from Group 3 (e.g. calcium D-glucarate); and d) one or more members selected from Group 4 (e.g. medium chain triglycerides).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); c) one or more members selected from Group 3 (e.g. calcium D-glucarate); and d) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 3 (e.g. calcium D-glucarate);

b) one or more members selected from Group 4 (e.g. medium chain triglycerides); and c) one or more members selected from Group 6 (e.g. lycopenes and carotenoids).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); c) one or more members selected from Group 4 (e.g. medium chain triglycerides); and d) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); c) one or more members selected from Group 3 (e.g. calcium D-glucarate); and d) one or more members selected from Group 6 (e.g. lycopenes and carotenoids).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 3 (e.g. calcium D-glucarate); c) one or more members selected from Group 4 (e.g. medium chain triglycerides); and d) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); c) one or more members selected from Group 4 (e.g. medium chain triglycerides); and d) one or more members selected from Group 6 (e.g. lycopenes and carotenoids).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); c) one or more members selected from Group 3 (e.g. calcium D-glucarate); d) one or more members selected from Group 4 (e.g. medium chain triglycerides); and e) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 3 (e.g. calcium D-glucarate); c) one or more members selected from Group 4 (e.g. medium chain triglycerides); and d) one or more members selected from Group 6 (e.g. lycopenes and carotenoids).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 3 (e.g. calcium D-glucarate); c) one or more members selected from Group 4 (e.g. medium chain triglycerides); and d) one or more members selected from Group 6 (e.g. lycopenes and carotenoids).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); c) one or more members selected from Group 3 (e.g. calcium D-glucarate); d) one or more members selected from Group 4 (e.g. medium chain triglycerides); and e) one or more members selected from Group 6 (e.g. lycopenes and carotenoids).

In one embodiment, this invention provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3: a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); c) one or more members

selected from Group 3 (e.g. calcium D-glucarate); d) one or more members selected from Group 4 (e.g. medium chain triglycerides); e) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline); and f) one or more members selected from Group 6 (e.g. lycopenes and carotenoids).

In one aspect, the term "at least one member" in reference to exemplary alternative embodiments comprises minimally every integer value from one to at 20, inclusive; i.e. in one aspect it means at least one member, in another aspect it means at least two members, in another aspect it means at least three members, ..., etc, and in another aspect it means at least 20 members. Alternative embodiments can comprise more than 20 members.

In one embodiment, this invention provides every combination and permutation of ingredients exemplified in Table 1 (i.e. Groups A-G). In another embodiment, this invention provides every combination and permutation of ingredients exemplified in from Table 3 (i.e. Groups 1-5).

In yet another embodiment, this invention provides every combination and permutation of ingredients selected from both Table 1 (i.e. Groups A-G) and Table 3 (Groups 1-5), particularly in a kit. For example, such a kit may have two preparations: 1) a preparation comprising ingredients from Table 1; and 2) a preparation comprising ingredients from Table 3; the two preparations may be physically separate; and, by way of non-limiting exemplification, the first preparation may be a liquid preparation that is consumed using a spoon, while the second preparation may be a preparation that is in the form of vegetable capsules (v-caps) that can be consumed like any capsule, tablet or pill.

In one embodiment, this invention provides a preparation of encapsulated bioavailable chelating agents comprising the following ingredients:

a) one or more members selected from a first group consisting of: R-(+)-alpha-lipoic acid (substantially enantiomerically pure), S-(-)-alpha-lipoic acid (substantially enantiomerically pure), R/S-alpha-lipoic acid (racemic mixture), R/S-gamma-lipoic acid (racemic mixture), other isomers of alpha lipoic acid, derivatives of alpha lipoic acid, dihydrolipoic acid (DHLA); wherein at least 1% of said one or more members from said first group is in microspheres or liposomes; and

b) one or more members selected from a second group consisting of: ethylene-diaminetetraacetic acid (EDTA), ethyleneglycol-bis[beta-aminoethyl ether]-N,N'-tetra-acetic acid (EGTA), diethylenetriamine-pentaacetic acid (DTPA), triethylenetetraaminehexaacetic acid (TTHA), N-hydroxyethylenediaminehexaacetic-acid

(HEDHA), 1,4,7-triazacyclononane-N,N',N"-triacetic acid (NOTA), 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA), N'-hydroxy-ethylenediamine-N,N,N'-triacetic acid (HEDTA), other polyaminopolycarboxylic acids, iminodiacetic acid (IDA), cyclam, penicillamine, dimercaptosuccinic acid, tartrate, thiomalic acid, crown ethers, nitrilotriacetatic acid (NTA), 3,6-dioxaoctanedithioamide, 3,6-dioxaoctanediamide, salicyladoximine, dithio-oxamide, 8-hydroxyquinoline, cupferron, 2,2'-thiobis(ethyl acetoacetate), 2,2'-dipyridyl; wherein at least 1% of said one or more members from said second group is in microspheres or liposomes; and

c) one or more members selected from a third group consisting of: lecithin, phophatidylcholine, phosphatidylserine, phosphatidylethanolamine, dilinoleylphosphatidylcholine, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, palmitic acid, stearic acid, oleic acid, linolenic acid, linoleic acid; wherein at least 1% of said one or more members from said third group is in a microsphere or a liposome.

This invention provides, in non-limiting embodiments, novel preparations of chelating agents encapsulated in micelles or liposomes comprising the triple combination of: 1) micelles or liposomes comprising alpha lipoic acid or a derivative thereof and 2) micelles or liposomes comprising a chelating agent, such as EDTA; and furthermore, in different embodiments, optionally 3) magnesium chloride. The micelles or liposomes can comprise what has been termed "essential phospholipids".

Biologically active and bioactive are used interchangeably, and can refer to *in vitro*, *ex vivo* and/or *in vivo* situations.

Physiological solutions suitable for intravenous injection or infusion include: e.g. Saline.

In one aspect, normal (physiologic) saline is used in the preparations and formulations of the invention. In alternative aspects, other pharmaceutically acceptable solutions can be utilized including, but not limited to, 0.9% saline solution, 5% dextrose solution, lactated Ringer's solution, 5% dextrose in lactated Ringer's solution, dextrose-saline combinations, albumin-containing solutions, dextran, dextran-saline combinations, etc. and equivalent solutions.

POEBACA: preparation(s) of encapsulated bioavailable chelating agents(s). Both plural and singular meanings are included.

POEBACAI: ingredient(s) for making up (a) preparation(s) of encapsulated bioavailable chelating agents(s). POEBACAI can exist in encapsulated form or in nonencapsulated form (e.g. a pre-encapsulated stage). Both plural and singular meanings are included.
1 ounce (oz.) = 28.3495231 grams (gm)
128 ounces = 1 gallon

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

All publications, patents and patent applications cited herein are hereby expressly incorporated by reference for all purposes.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides novel preparations of encapsulated bioavailable chelating agents (e.g., "POEBACA"). Alternative embodiments of POEBACA comprise the following ingredients (or "PEOBACAI"), for which non-limiting examples are listed in Table 1:

a) one or more members selected from Group A (e.g. alpha lipoic acid); b) one or more members selected from Group B (e.g. EDTA); c) one or more members selected from Group C (e.g. lecithin); d) optionally, in separate embodiments, one or more members selected from Group D (e.g. magnesium chloride); e) optionally, in separate embodiments, one or more members selected from Group E (glutathione); f) optionally, in separate embodiments, one or more members selected from Group F (e.g. vinpocetine); g) optionally, in separate embodiments, one or more members selected from Group G (e.g. nitrogen gas); wherein the ingredients are prepared in a manner that provides the encapsulation of a significant fraction of one or more ingredient(s) into liposomes or microspheres.

This invention also provides novel preparations comprising the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

a) one or more members selected from Group 1 (e.g. DIM); b) one or more members selected from Group 2 (e.g. grape extract or grape skin extract or wine extract, e.g. red wine extract,, resveratrol, and piceatannol); c) one or more members selected

from Group 3 (e.g. calcium D-glucarate); d) one or more members selected from Group 4 (e.g. medium chain triglycerides); e) optionally, in separate embodiments, one or more members selected from Group 5 (e.g. lecithin).

In one embodiment, this invention provides that a serviceable ingredient that is a member of Group 4, can be a preparation in which at least half of the content by weight is MCTs, said at least half of the content by weight of MCTs comprising at least about 40% MCTs having lengths between C_5 and C_{11}. In separate embodiments, said at least half of the content by weight of MCTs can range from at least about 40% to at least about 95% (also including every integer value in this range) MCTs having lengths between C_5 and C_{11}. Thus, for example, this invention provides that a serviceable ingredient that is a member of Group 4, can be a preparation in which at least half of the content by weight is MCTs, said at least half of the content by weight of MCTs comprising at least about 90% MCTs having lengths between C_5 and C_{11}.

Exemplary numbers of Group A members (e.g. alpha lipoic acid).

In alternative embodiments "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided, each of which comprises at least a minimum number of members, i.e. "n" member(s), selected from Group A, where n = 1, 2, 3, ..., 100, including every integer value within the range of 1 to 100. Thus, there are at least 100 embodiments of POEBACA, differing in that the minimum number of members selected from Group A that is contained in each embodiment ranges from one to one hundred (including every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 100. Thus, one alternative embodiment of this invention provides a POEBACA comprising at least one member selected from Group A; another alternative embodiment of this invention provides a POEBACA comprising at least two members selected from Group A; another alternative embodiment of this invention provides a POEBACA comprising at least three members selected from Group A; etc. ; another alternative embodiment of this invention provides a POEBACA comprising at least one hundred members selected from Group A; for convenience these are referred to as alternative embodiments A1 to A100, and these separate embodiments are intended to be the subject matter of separate claims according to this invention.

Exemplary numbers of Group B members (e.g. EDTA).

In alternative embodiments "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided, each of which comprises at least a minimum number of members, i.e. "n" member(s), selected from Group B, where n = 1, 2, 3, ...,

100, including every integer value within the range of 1 to 100. Thus, there are at least 100 embodiments of POEBACA, differing in that the minimum number of members selected from Group B that is contained in each embodiment ranges from one to one hundred (including every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 100. Thus, one alternative embodiment of this invention provides a POEBACA comprising at least one member selected from Group B; another alternative embodiment of this invention provides a POEBACA comprising at least two members selected from Group B; another alternative embodiment of this invention provides a POEBACA comprising at least three members selected from Group B; etc. ; another alternative embodiment of this invention provides a POEBACA comprising at least one hundred members selected from Group B; for convenience these are referred to as alternative embodiments B1 to B100, and these separate embodiments are intended to be the subject matter of separate claims according to this invention.

Exemplary numbers of Group C members (e.g. lecithin).

In alternative embodiments of "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided, each of which comprises at least a minimum number of members, i.e. "n" member(s), selected from Group C, where n = 1, 2, 3, ..., 100, including every integer value within the range of 1 to 100. Thus, there are at least 100 embodiments of POEBACA, differing in that the minimum number of members selected from Group C that is contained in each embodiment ranges from one to one hundred (with every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 100. Thus, one alternative embodiment of this invention provides a POEBACA comprising at least one member selected from Group C; another alternative embodiment of this invention provides a POEBACA comprising at least two members selected from Group C; another alternative embodiment of this invention provides a POEBACA comprising at least three members selected from Group C; etc. ; another alternative embodiment of this invention provides a POEBACA comprising at least one hundred members selected from Group C; for convenience these are referred to as alternative embodiments C1 to 100, and these separate embodiments are intended to be the subject matter of separate claims according to this invention.

Group D members (e.g. magnesium chloride).

In one aspect, "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided herein, each of which comprises at least a minimum number of members, i.e. "n" member(s), selected from Group D, where n = 1, 2, 3, ..., 20, including

every integer value within the range of 1 to 20. Thus, there are at least 20 embodiments of POEBACA, differing in that the minimum number of members selected from Group D that is contained in each embodiment ranges from one to twenty (including every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 20. Thus, one alternative embodiment of this invention provides a POEBACA comprising at least one member selected from Group D; another alternative embodiment of this invention provides a POEBACA comprising at least two members selected from Group D; another alternative embodiment of this invention provides a POEBACA comprising at least three members selected from Group D; etc. ; another alternative embodiment of this invention provides a POEBACA comprising at least twenty members selected from Group D; for convenience these are referred to as alternative embodiments D1 to D20, and these separate embodiments are intended to be the subject matter of separate claims according to this invention.

Exemplary numbers of Group E members (e.g. glutathione).

In alternative embodiments "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided, each of which comprises at least a minimum number of members, i.e. "n" member(s), selected from Group E, where n = 1, 2, 3, ..., 20, including every integer value within the range of 1 to 20. Thus, there are at least 20 embodiments of POEBACA, differing in that the minimum number of members selected from Group E that is contained in each embodiment ranges from one to twenty (including every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 20. Thus, one alternative embodiment of this invention provides a POEBACA comprising at least one member selected from Group E; another alternative embodiment of this invention provides a POEBACA comprising at least two members selected from Group E; another alternative embodiment of this invention provides a POEBACA comprising at least three members selected from Group E; etc. ; another alternative embodiment of this invention provides a POEBACA comprising at least twenty members selected from Group E; for convenience these are referred to as alternative embodiments E1 to E20, and are intended to be claimed subject matter according to this invention.

Exemplary numbers of Group F members (e.g. vinpocetine).

In alternative embodiments "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided, each of which comprises at least a minimum number of members, i.e. "n" member(s), selected from Group F, where n = 1, 2, 3, ..., 20,

including every integer value within the range of 1 to 20. Thus, there are at least 20 embodiments of POEBACA, differing in that the minimum number of members selected from Group F that is contained in each embodiment ranges from one to twenty (including every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 20. Thus, one alternative embodiment of this invention provides a POEBACA comprising at least one member selected from Group F; another alternative embodiment of this invention provides a POEBACA comprising at least two members selected from Group F; another alternative embodiment of this invention provides a POEBACA comprising at least three members selected from Group F; etc. ; another alternative embodiment of this invention provides a POEBACA comprising at least twenty members selected from Group F; for convenience these are referred to as alternative embodiments F1 to F20, and these separate embodiments are intended to be the subject matter of separate claims according to this invention.

Alternative numbers of Group G members (e.g. nitrogen gas).

In alternative embodiments "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided, each of which comprises at least a minimum number of members, i.e. "n" member(s), selected from Group G, where n = 1, 2, 3, ..., 20, including every integer value within the range of 1 to 20. Thus, there are at least 20 embodiments of POEBACA, differing in that the minimum number of members selected from Group G that is contained in each embodiment ranges from one to twenty (including every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 20. Thus, one alternative embodiment of this invention provides a POEBACA comprising at least one member selected from Group G; another alternative embodiment of this invention provides a POEBACA comprising at least two members selected from Group G; another alternative embodiment of this invention provides a POEBACA comprising at least three members selected from Group G; etc. ; another alternative embodiment of this invention provides a POEBACA comprising at least twenty members selected from Group G; for convenience these are referred to as alternative embodiments G1 to G20, and these separate embodiments are intended to be the subject matter of separate claims according to this invention.

Exemplary numbers of members from Groups A through G.

This invention further provides the additional aspects that result from all the possible combinations and permutations of the alternative embodiments of A1 to A100, B1 to B100, C1 to C100, D1 to D20, E1 to E20, F1 to F20, and G1 to G20. By way of

illustration, (100 alternative embodiments corresponding to A1 to A100) x (100 alternative embodiments corresponding to B1 to B100) x (100 alternative embodiments corresponding to C1 to C100) x (20 alternative embodiments corresponding to D1 to D20) x (20 alternative embodiments corresponding to E1 to E20) x (20 alternative embodiments corresponding to F1 to F100) x (100 alternative embodiments corresponding to G1 to G20) = 160,000,000,000 or one hundred and sixty billion alternative aspects, and these separate aspects are intended to be the subject matter of separate claims according to this invention.

Exemplary amounts of ingredients.

In alternative aspects, the relative amounts of each ingredient that can comprise a POEBACA according to this invention are illustrated in Table 2. In separate embodiments, this invention provides all the physically possible combinations and permutations of ingredient amounts that listed in Table 2. Thus, this invention provides that the relative amounts of these ingredients can vary (as illustrated in Table 2), yielding additional aspects. Therefore, when considering the claim limitations regarding the relative amount of ingredients, the number of alternative embodiments is greater, by orders of magnitude, than 160,000,000,000 or one hundred and sixty billion alternative embodiments that don't specify amounts of ingredients, and all these alternative embodiments are intended to be the subject matter of separate claims according to this invention.

Table 1 describes alternative ingredients used in the compositions and methods of the invention.

Table 1: Exemplary ingredients used in the methods and compositions of the invention.

Group	Group Members (Non-limiting examples are listed for each group)
A	Antioxidants and hydrophobic ingredients R-(+)-alpha-lipoic acid (substantially enantiomerically pure), S-(-)-alpha-lipoic acid (substantially enantiomerically pure), R/S-alpha-lipoic acid (racemic mixture), R/S-gamma-lipoic acid (racemic mixture), other isomers of alpha lipoic acid, derivatives of alpha lipoic acid (such as the dihydro version of these alpha lipoic acid isomers, also known as dihydrolipoic acid or DHLA), animal and vegetable oils, hydrocarbon oils, ester oils, silicone oils, higher fatty acids, higher alcohols, sunscreening agents, vitamins, ferulic acid

B	Chelators EDTA, EGTA, DPTA, TTHA, HEDHA, NOTA, DOTA, HEDTA, other polyaminopolycarboxylic acids, iminodiacetic acid (IDA), cyclam, penicillamine, dimercaptosuccinic acid, tartrate, thiomalic acid, crown ethers, nitrilotriacetatic acid (NTA), 3,6-dioxaoctanedithioamide, 3,6-dioxaoctanediamide, salicyladoximine, dithio-oxamide, 8-hydroxyquinoline, cupferron, 2,2'-thiobis(ethyl acetoacetate), 2,2'-dipyridyl, and derivatives thereof
C	Phospholipids, lipids and fatty acids lecithin, phophatidylcholine, phosphatidylserine, phosphatidylethanolamine, dilinoleylphosphatidylcholine, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, fatty acids (e.g. palmitic acid, stearic acid, oleic acid, linolenic acid, linoleic acid, etc.), glycosphingolipids, glucolipids, glycolipids, sulphatides, lipids bearing sulfonated mono-, di-, oligo- or polysaccharides, lipids with ether and ester-linked fatty acids, triglycerides, lipoproteins (high or low density), cholesterol, and other lipids and polymerized lipids. In one aspect, lecithin that contains at least 20% phosphatidyl choline (this invention provides separate embodiments where the lecithin content of phosphatidyl choline is approximately each integer value between 20% and 90%).
D	Magnesium Salts Magnesium chloride, Magnesium Gluconate, Magnesium Carbonate, Calcium Magnesium Citrate, Magnesium Sulfate
E	Sulfur-Containing Amino Acids, Sulfur-Containing Peptides, Sulfur-Containing Proteins Glutathione, methionine, cysteine
F	Plant alkaloids (e.g. vinpocetine, vincamine), coenzyme Q10, and analogues coenzyme Q10 (e.g. idebenone)
G	Gaseous ingredient Nitrogen gas, oxygen gas, atmospheric air, gaseous mixtures containing nitrogen gas, gaseous mixtures containing oxygen gas.

Table 2. Amounts of ingredients to be protected as claimed by this invention. Values are normalized to 2 oz or approximately 56 grams.

Group (with example of a group member)	Example 1 (Absolute amount, mg)	Example 1 (Relative amount, %)	Alternative amounts intended for protection according to this invention (both individually and collectively as a group)
A (e.g. alpha lipoic acid)	100.0 mg	0.17	From about 0.01 mg to about 20,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.
B (e.g. EDTA)	1,000.0 mg	1.7	From about 0.01 mg to about 30,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.
C (e.g. lecithin)	30,000.0 mg	50.0	From about 0.01 mg to about 40,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.
D (e.g. magnesium chloride)	150.0 mg	0.26	From about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.
E (e.g. glutathione)	1,000mg	1.7	From about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.
F (e.g. vinpocetine)	100 mg	0.17	From about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.
Example 1. Other ingredients: Water (30 – 40%), Ethanol (5 – 15 %), Gum Arabic (0.5 – 2%), Flavorings (0 – 5 %).			

Table 3: Exemplary ingredients used in the methods and compositions of the invention. (See Table 4 for alternative amounts according to this invention)

Group	Group Members (Non-limiting examples are listed for each group)

Group	Group Members (Non-limiting examples are listed for each group)
1	Plant indoles, including sources of plant indoles (e.g. DIM). Sources of plant indoles include including vegetables, as well as parts thereof (e.g. skin, flesh, seeds, etc.) and extracts thereof (e.g. skin extracts), belonging to or related to the mustard family (Cruciferae or Brassicaceae), which includes the alyssum, candytuft, cabbage, radish, broccoli, and many weeds. DIM is also found in grapes, teas (e.g. black teas), cranberry, cherries, blackberries and other berries. E.g. Indole-3-carbinol (I3C) and its dimer 3,3'-diindolylmethane (DIM). It is appreciated that substances such as I3C and DIM can be modified or derivatized (form a chemical point of view), and both the alternative use of and the additional use of these modified or derivatized substances are also protected by this invention. Diindolylmethane, or DIM, and Indole-3-carbinol (I3C) can be isolated from or found in cruciferous vegetables, or, be synthetic

Group	Group Members (Non-limiting examples are listed for each group)
2	Plant flavonoids, polyphenols, stilbenes and related substances (PFPSARS), including sources of plant flavonoids, polyphenols, stilbenes, and related substances (e.g. 3,5,4′-trihydroxy stilbene or resveratrol, piceatannol, and grape extract or grape skin extract or wine extract, e.g. red wine extract). Sources of plant polyphenols include at least 70 to 80 species (if not a lot more), e.g. mulberries, peanuts, and grapes, as well as parts thereof (e.g. skin, flesh, seeds, etc.) and extracts thereof (e.g. skin extracts such as curcumin skin extract and grape extract or grape skin extract or wine extract, e.g. red wine extract,), as well as in wines and vinegars. PFPSARS are also found, by way of non-limiting examples, in a) Piper methysticum, kava kava, Piperaceae, plant in flower; b) Pinus resinosa, red pine, Pinaceae, trees in forest; c) Saccharum officinarum, sugar cane, Poaceae, drawing; d) Vitis vinifera, grape, Vitaceae, fruits; Morus alba, mulberry, Moraceae, male and female flowers; e) Marchantia polymorpha, a liverwort, gametophytes and sporophytes; f) Orchis militaris, Helm Knabenkraut, Orchidaceae, flowers; and g) huzhang (Polygonum cuspidatum aka "tiger cane" or giant knotweed). E.g. Resveratrol and its metabolite piceatannol. It is appreciated that substances such as resveratrol and piceatannol can be modified or derivatized (form a chemical point of view), and both the alternative use of and the additional use of these modified or derivatized substances are also protected by this invention.

Group	Group Members (Non-limiting examples are listed for each group)
3	Glucaric acid and derivatives thereof (e.g. calcium d-glucarate and 1,4-GL) including sources thereof. Calcium D-glucarate is the calcium salt of D-glucaric acid, a natural substance found in many fruits and vegetables. It is appreciated that different salt of D-glucaric acid exist (e.g. potassium hydrogen D-glucarate or PHG), and that D-glucaric acid can be modified or derivatized (form a chemical point of view), and both the alternative use of and the additional use of these different salts or derivatized substances (e.g. D-glucaro-l,4-lactone or 1,4-GL, 2-keto-3-deoxy-D-glucarate, and 4-deoxy-5-keto-D-glucarate) are also protected by this invention.

Group	Group Members (Non-limiting examples are listed for each group)
4	Medium Chain Triglycerides and sources thereof (e.g. a preparation in which at least half of the content by weight is MCT, said at least half of the content comprising at least 80% between C_5 and C_{11} MCTs). Sources of medium chain triglycerides or MCTs include coconut oil, palm kernel oil, camphor tree drupes, and butter. MCT are also available as a supplement. Medium chain triglycerides are medium-chain fatty acid esters of glycerol. Medium-chain fatty acids are fatty acids containing from six to 12 carbon atoms. Coconut and palm kernel oils are also called lauric oils because of their high content of the 12 carbon fatty acid, lauric or dodecanoic acid. Medium-chain triglycerides used for nutritional and other commercial purposes are sometimes derived from lauric oils. In the process of producing MCTs, lauric oils are hydrolyzed to medium-chain fatty acids and glycerol. The glycerol is drawn off from the resultant mixture, and the medium-chain fatty acids are fractionally distilled. The medium-chain fatty acid fraction used commercially is sometimes mainly comprising the eight carbon caprylic or octanoic acid and the 10 carbon capric or decanoic acid. There are much smaller amounts of the six carbon caproic or hexanoic acid and the 12 carbon lauric acid in the commercial products. The caprylic- and capric-rich mixture is finally re-esterified to glycerol to produce medium-chain triglycerides that are mainly glycerol esters of caproic (C_6) caprylic (C_8), capric (C_{10}) and lauric acid (C_{12}) in a ratio of approximately 2:55:42:1. MCTs have chemical structures well known in the art.

Group	Group Members (Non-limiting examples are listed for each group)
5	Phospholipids and sources thereof (e.g. lecithin) Examples include lecithin, phophatidylcholine, phosphatidylserine, phosphatidylethanolamine, dilinoleylphosphatidylcholine, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, fatty acids (e.g. palmitic acid, stearic acid, oleic acid, linolenic acid, linoleic acid, etc.), glycosphingolipids, glucolipids, glycolipids, sulphatides, lipids bearing sulfonated mono-, di-, oligo- or polysaccharides, lipids with ether and ester-linked fatty acids, triglycerides, lipoproteins (high or low density), cholesterol, and other lipids and polymerized lipids.
6	Lycopenes and carotenoids (carotenes and xanthophylls) and sources thereof Examples include alpha-carotene, beta-carotene, lutein, cyptoxanthin, zeaxanthin and plant-derived lycopenes (e.g. blueberry-derived and tomato-derived lycopenes).

Table 4. Amounts of ingredients used in compositions and methods of the invention. Values are normalized to a "00" capsule, containing approximately 800 mg total (typically in the range of approximately 700 – 900 mg).

Group (with example of a group member)	Example 4 (Absolute amount, mg)	Example 4 (Relative amount, %, assuming approx. 800 mg total)	Alternative amounts intended for protection as claimed according to this invention (both individually and collectively as a group)
1 (e.g. DIM)	100 mg	12.5	From about 0.01 mg to about 600 mg inclusive, including specifically each increment of about 0.01 mg within this range.

2 (e.g. Grape extract or grape skin extract or wine extract, e.g. red wine extract, and resveratrol)	200 mg	25.0	From about 0.01 mg to about 600 mg inclusive, including specifically each increment of about 0.01 mg within this range.
3 (e.g. calcium D-Glucarate)	200 mg	25.0	From about 0.01 mg to about 600 mg inclusive, including specifically each increment of about 0.01 mg within this range.
4 (e.g. medium chain triglycerides)	50 mg	6.25	From about 0.01 mg to about 600 mg inclusive, including specifically each increment of about 0.01 mg within this range.
5 (e.g. lecithin and phosphatidyl)	50mg	6.25	From about 0.01 mg to about 600 mg inclusive, including specifically each increment of about 0.01 mg within this range.
6 (e.g. lycopenes and carotenoids)	50 mg	6.25	From about 0.01 mg to about 600 mg inclusive, including specifically each increment of about 0.01 mg within this range.
Example 4. Other optional ingredients: Cellulose powder (1-20%), Magnesium silicate (1 – 20 %), Magnesium stearate (0.1 -10%), Silicon dioxide (0.1-10%), Gum Acacia (0.1-10%), Other flavorings (0 – 10 %).			

This invention provides alternative embodiments wherein the instant preparations comprise ingredients exemplified in Table 1, and, in one aspect, are orally ingestible. In a non-limiting exemplification these preparations can be liquids (e.g. that can be orally ingested with the help of a spoon), or capsules, tablets, and pills. In non-limiting exemplifications, they can also be formed into flavored bars (e.g. similar to what bars that are marketed as "power bars", "diet bars", "energy bars", and "nutritional bars").

This invention provides that the instant preparations comprising ingredients exemplified in Table 3 are orally ingestible. In a non-limiting exemplification these preparations can be liquids (e.g. that can be orally ingested with the help of a spoon), or capsules, tablets, and pills. In non-limiting exemplifications, they can also be formed into flavored bars (e.g. similar to what bars that are marketed as "power bars", "diet bars", "energy bars", and "nutritional bars").

This invention provides that the ingredients required herein, such as the ingredients exemplified in Table 1 and in Table 3 (for making the instant preparations) are ingredients that are commercially available from numerous commercial sources. E.g. grape extract or grape skin extract or wine extract, e.g. red wine extract, have been known; edible grape extract or grape skin extract or wine extract, e.g. red wine extract, is discussed in 21 CFR Sec. 73.170, where Grape extract or grape skin extract or wine extract, e.g. red wine extract, is also termed enocianina.

In Table 2 the relative amounts of each ingredient (POEBACAI) have been expressed in the context of a 2 ounce dose. This is for convenience and consistency, but in separate embodiments this invention provides that that dosages or other sizes can be prepared and administered, particularly ranging, by way of non-limiting exemplification, from about 0.1 ounce to about 128 ounces (or one gallon), including every 0.1 ounce increment in between.

Alternative amount(s) of Group A members (e.g. alpha lipoic acid).

This invention provides separate embodiments wherein per 2 ounces the total amount of ingredient(s) from Group A (e.g. alpha lipoic acid) collectively is from about 0.01 mg to about 20,000 mg inclusive, including specifically each increment of about 0.01 mg within this range. Furthermore, this invention provides separate embodiments wherein per 2 ounces the total amount of each specific Group A ingredient(s) individually is from about 0.01 mg to about 20,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.

Thus; by way of illustration:

1) in one embodiment, this invention provides preparations of encapsulated bioavailable chelating agents (i.e. POEBACA) wherein the total amount of Group A members (e.g. alpha lipoic acid) is about 0.01 mg;

2) in another embodiment, this invention provides preparations of encapsulated bioavailable chelating agents (i.e. POEBACA) wherein the total amount of Group A members (e.g. alpha lipoic acid) is about 0.02 mg;

3) in another embodiment, this invention provides preparations of encapsulated bioavailable chelating agents (i.e. POEBACA) wherein the total amount of Group A members (e.g. alpha lipoic acid) is about 0.03 mg; etc.; and

4) in another embodiment, this invention provides preparations of encapsulated bioavailable chelating agents (i.e. POEBACA) wherein the total amount of Group A members (e.g. alpha lipoic acid) is about 20,000 mg.

Thus, there are at least 2,000,000 alternative embodiments. This is illustrated in Table 2.

Alternative amount(s) of Group B members (e.g. EDTA).

This invention provides separate embodiments wherein per 2 ounces the total amount of ingredient(s) from Group B (e.g. EDTA) collectively is from about 0.01 mg to about 30,000 mg inclusive, including specifically each increment of about 0.01 mg within this range. Furthermore, this invention provides separate embodiments wherein per 2 ounces the total amount of each specific Group B ingredient(s) individually is from about 0.01 mg to about 30,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.

Alternative amount(s) of Group C members (e.g. lecithin).

This invention provides separate embodiments wherein per 2 ounces the total amount of ingredient(s) from Group C (e.g. lecithin) collectively is from about 0.01 mg to about 40,000 mg inclusive, including specifically each increment of about 0.01 mg within this range. Furthermore, this invention provides separate embodiments wherein per 2 fluid ounces the total amount of each specific Group C ingredient(s) individually is from about 0.01 mg to about 40,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.

Alternative amount(s) of Group D members (e.g. magnesium chloride).

This invention provides separate embodiments wherein per 2 ounces the total amount of ingredient(s) from Group D (e.g. magnesium chloride) collectively is from about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range. Furthermore, this invention provides separate embodiments wherein per 2 ounces the total amount of each specific Group D ingredient(s) individually is from about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.

Alternative amount(s) of Group E members (e.g. glutathione).

This invention provides separate embodiments wherein per 2 ounces the total amount of ingredient(s) from Group E (e.g. glutathione) collectively is from about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range. Furthermore, this invention provides separate embodiments wherein per 2 fluid ounces the total amount of each specific Group E ingredient(s) individually is from about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.

Alternative amount(s) of Group F members (e.g. vinpocetine).

This invention provides separate embodiments wherein per 2 ounces the total amount of ingredient(s) from Group F (e.g. vinpocetine) collectively is from about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range. Furthermore, this invention provides separate embodiments wherein per 2 ounces the total amount of each specific Group F ingredient(s) individually is from about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.

Alternative percentages of encapsulated Group G members (e.g. nitrogen gas).

This invention provides separate embodiments wherein one or more gases may be contained in a percentage of the liposomes or micropsheres in a POEBACA. In alternative embodiments, the gas comprises nitrogen gas, oxygen gas, atmospheric air, gaseous mixtures containing nitrogen gas, gaseous mixtures containing oxygen gas, or a combination thereof. In separate embodiments, the percent of liposomes or micropsheres that contains a gas is from about 1% to about 100%, including every integer value in between.

Alternative methods of administration.

This invention provides POEBACA that can be administered by several routes, including intravenous, topical, and oral. Furthermore, in separate embodiments, this invention provides forms of POEBACA that can be administered by inoculation, infusion or injection, (e.g., intraperitoneal, intramuscular, subcutaneous, intra-aural, intra-articular, intra-mammary, etc.), topical application (e.g., on areas, such as eyes, ears, skin or on afflictions such as wounds, burns, etc.), and by absorption through epithelial or mucocutaneous linings (e.g. vaginal and other epithelial linings, gastrointestinal mucosa, etc.). Methods are known for making POEBACA containing liposomes that are suitable for each of these methods of administration as well as other methods of administration that are know in the art.

For example, in alternative embodiments, this invention provides POEBACA in liquid forms that can be administered orally. The POEBACA can be also prepared as capsules, tablets, powders, sprays, aerosols, pellets (e.g. for animal consumption), suppositories, or creams and ointments. The POEBACA can be also prepared as physiological solutions suitable for I.V. administration or other parenteral administration.

In as many separate aspects, this invention also provides all the possible combinations of ingredient quantities that are possible (e.g. the total of all the ingredients

or POEBACAI does not surpass 100% of the relevant total dosage of the POEBACA, and admixing or solubility limitations are not exceeded).

Alternative percentages of ingredients that are contained in liposomes or micropsheres.

In separate aspects, this invention also provides that a POEBACA may include ingredients (or POEBACAI) that are not contained in micropsheres or liposomes in addition to ingredients that are contained in liposomes, and that these ingredients may be the same or different substances.

In separate aspects, this invention also provides that for each ingredient (or POEBACAI) the percent that is contained in micropsheres or liposomes (in contrast to the percentage that is not contained in micropsheres or liposomes, but rather is in solution) may be from about 0.1% to about 100.0%, including every 0.1% increment within this range. This provides at least about 1000 separate aspects that are intended for protection according to this invention.

In separate aspects, this invention also provides that in a single POEBACA, the micropsheres or liposomes may be fairly homogeneous in size or in content; alternatively they may be fairly heterogeneous in size or in content.

Alternative Group A members (e.g. alpha lipoic acid).

In one aspect, Group A members include: antioxidants, particularly hydrophobic antioxidants and other hydrophobic ingredients.

Group A members include, but are not limited to: R-(+)-alpha-lipoic acid (substantially enantiomerically pure), S-(-)-alpha-lipoic acid (substantially enantiomerically pure), R/S-alpha-lipoic acid (racemic mixture), R/S-gamma-lipoic acid (racemic mixture), other isomers of alpha lipoic acid, derivatives of alpha lipoic acid (such as the dihydro version of these alpha lipoic acid isomers, also known as dihydrolipoic acid or DHLA), animal and vegetable oils, hydrocarbon oils, ester oils, silicone oils, higher fatty acids, higher alcohols, sunscreening agents, vitamins, ferulic acid and equivalent compounds.

Group A members also include, but are not limited to: fatty acids, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, glycosphingolipids, glucolipids, glycolipids, sulphatides, lipids bearing sulfonated mono-, di-, oligo- or polysaccharides, lipids with ether and ester-linked fatty acids, and polymerized lipids and equivalent compounds.

Alternative Group B members (e.g. EDTA).

In one aspect, Group B members include: chelators or chelating agents. Group B members include, but are not limited to: EDTA, EGTA, DPTA, TTHA, HEDHA, NOTA, DOTA, HEDTA, other polyaminopolycarboxylic acids, iminodiacetic acid (IDA), cyclam, penicillamine, dimercaptosuccinic acid, tartrate, thiomalic acid, crown ethers, nitrilotriacetatic acid (NTA), 3,6-dioxaoctanedithioamide, 3,6-dioxaoctanediamide, salicyladoximine, dithio-oxamide, 8-hydroxyquinoline, cupferron, 2,2'-thiobis(ethyl acetoacetate), 2,2'-dipyridyl, and derivatives thereof and equivalent compounds. According to this invention, other chelators that are members of Group B are provided herein or are otherwise known in the art and can serve as ingredients for this invention.

Alternative Group C members (e.g. lecithin).

In one aspect, Group C members include: phospholipids, lipids and fatty acids. Group C members include, but are not limited to: lecithin, phophatidylcholine, phosphatidylserine, phosphatidylethanolamine, dilinoleylphosphatidylcholine, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, fatty acids (e.g. palmitic acid, stearic acid, oleic acid, linolenic acid, linoleic acid, etc.), glycosphingolipids, glucolipids, glycolipids, sulphatides, lipids bearing sulfonated mono-, di-, oligo- or polysaccharides, lipids with ether and ester-linked fatty acids, triglycerides, lipoproteins (high or low density), cholesterol, and other lipids and polymerized lipids and equivalent compounds.

Alternative Group D members (e.g. magnesium chloride).

In one aspect, Group D members include: magnesium salts. Group D members include, but are not limited to: magnesium chloride, magnesium gluconate, magnesium carbonate, calcium magnesium citrate, magnesium sulfate, other salts of magnesium, and other forms of magnesium and equivalent compounds.

Alternative Group E embers (e.g. glutathione).

In one aspect, Group E embers include: sulfur-containing amino acids, sulfur-containing peptides, sulfur-containing proteins, and other sulfur-containing substances. Group E members include, but are not limited to: glutathione, methionine, cysteine, glutathione-containing peptides and proteins, methionine-containing peptides and proteins, cysteine-containing peptides and proteins, glutathione-containing substances, methionine-containing substances, cysteine-containing substances and equivalent compounds.

Alternative Group F members (e.g. vinpocetine).

In one aspect, Group F members include: Vinpocetine, vincamine, idebenone and equivalent compounds.

Alternative Group G members (e.g. nitrogen gas).

In one aspect, Group G members include: Nitrogen gas, atmospheric air, and other mixtures of gases that contain nitrogen, oxygen, mixtures of gases that contain oxygen, argon, and mixtures of gases that contain argon, etc. and equivalent compounds

Lipophilic Anti-oxidants (e.g. alpha lipoic acid).

In one aspect, the compositions and methods of the invention use alpha-lipoic acid; which in addition to its non-toxicity and lipophilicity has the advantage of being rapidly converted in tissues into its reduced form, dihydrolipoic acid (DHLA). DHLA also has potent antioxidant effects. Further, both alpha-lipoic acid and DHLA have been shown to disarm oxidants through a variety of mechanisms including free radical quenching, metal chelation, and regeneration of other common natural antioxidants.

In one embodiment, the present invention provides a lipophilic antioxidant in an aqueous physiological fluid, such as a resuscitation fluid by lipid encapsulation, e.g. by providing liposomal formation methods to form stable micellular solutions of alpha-lipoic acid or other lipophilic antioxidant(s).

In one aspect, the present invention seeks to overcome previous limitations by solubilizing alpha-lipoic acid in aqueous solution without the use of solvents such as harsh organic solvents. Alpha-lipoic acid and other antioxidants are rendered soluble in aqueous solutions by the use of liposomal formation processes, such as ultrasonication. Because the .alpha.-lipoic molecule contains a polar (water soluble) carboxy-acid group and a non-polar, lipid soluble chain of carbon and sulfur atoms, the molecule is amphipathic, i.e., it has the ability to form micelles. Micelles may be formed in aqueous solution if a molecule possesses both polar and non-polar groups. After ultrasonication the polar, a number of the water soluble ends of the alpha-lipoic acid molecule are on the outside of aggregations of alpha-lipoic acid. A number of the non-polar, lipid soluble tails are directed inward forming a tiny droplet, a micelle, which is water soluble. Ultrasonication of amphipathic molecules into micelles such as can be done with alpha-lipoic acid also has the possibility of creating mixed micelles. In this manner a mixture of alpha-lipoic acid with other antioxidants, which may not have the ability to form micelles alone for lack of any polar group, can be contained within a micelle of alpha-lipoic acid.

In this way, mixed micelles containing alpha-lipoic acid and purely non-polar but highly lipid soluble antioxidants can be used to convey antioxidants to the tissues.

There are numerous other clinical conditions in addition to hemorrhagic shock which have as their final common pathway oxidant-inducing injury to tissues and can be ameliorated (e.g., treated) and/or prevented with the compositions and methods of the invention.

CHELATING AGENTS

In one aspect, various chelating agents are used in the compositions and methods of the invention. For example, in one aspect, polyaminopolycarboxylic acid or EDTA (ethylene-diaminetetraacetic acid) are provided as a chelating agent for removing toxins such as heavy metals. Additionally, a related polyaminopolycarboxylic acid, diethylenetriaminepentaacetic acid (DTPA) is also provided as a chelating agent that has been shown to have an ability to remove various heavy metals.

In one aspect, EGTA (ethyleneglycol-bis[.beta.-aminoethyl ether]-N,N'-tetra-acetic acid) is also provided as chelating agent. EGTA is more specific for particular substances such as calcium when compared to other substances such as magnesium, and thus may be used as a alternative ingredient when it is desirable to chelate calcium (e.g. as is found in arterial plaques, and thus for diminishing arterial plaques) more than for chelating magnesium.

In one aspect, DMSA (dimercaptosuccinic acid) is used; it is one effective oral chelating agent that is absorbed orally, and is more effective at chelating particular substances such as mercury, cadmium, lead, and arsenic in comparison to other substances; and thus DMSA may be used as a alternative ingredient when it is desirable to chelate mercury, cadmium, lead and arsenic (such for the detoxification of poisoning from lead, mercury, cadmium or arsenic) more than for chelating other substances.

Other useful chelating agents are also provided and used in the compositions and methods of the invention, including diethylenetriamine-pentaacetic acid (DTPA), triethylenetetraaminehexaacetic acid (TTHA), N-hydroxyethylenediaminehexaacetic-acid (HEDHA), 1,4,7-triazacyclononane-N,N',N''-triacetic acid (NOTA), 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA), and N'-hydroxy-ethylenediamine-N,N,N'-triacetic acid (HEDTA).

Alternative chelating agents used in the compositions and methods of the invention include iminodiacetic acid (IDA), cyclam, penicillamine, dimercaptosuccinic

acid, tartrate, thiomalic acid, crown ethers, nitrilotriacetatic acid (NTA), 3,6-dioxaoctanedithioamide, 3,6-dioxaoctanediamide, salicyladoximine, dithio-oxamide, 8-hydroxyquinoline, cupferron, 2,2'-thiobis(ethyl acetoacetate), 2,2'-dipyridyl. IDA is a alternative chelating headgroup which is selective for copper ions.

Exemplary chelators for use in the present invention include, but are not limited to, ethylenediamine-N,N,N',N'-tetraacetic acid (EDTA); the disodium, trisodium, tetrasodium, dipotassium, tri-potassium, dilithium and diammonium salts of EDTA; the barium, calcium, cobalt, copper, dysprosium, europium, iron, indium, lanthanum, magnesium, manganese, nickel, samarium, strontium, and zinc chelates of EDTA; trans-1,2-diaminocyclohexane-N,N,N',N'-tetraaceticacid monohydrate; N,N-bis(2-hydroxyethyl)glycine; 1,3-diamino-2-hydroxypropane-N,N,N',N'-tetraacetic acid; 1,3-diaminopropane-N,N,N',N'-tetraacetic acid; ethylenediamine-N,N'-diacetic acid; ethylenediamine-N,N'-dipropionic acid dihydrochloride; ethylenediamine-N,N'-bis(methylenephosphonic acid) hemihydrate; N-(2-hydroxyethyl)ethylenediamine-N,N',N'-triacetic acid; ethylenediamine-N,N,N',N'-tetrakis(methylenephosponic acid); O,O'-bis(2-aminoethyl)ethyleneglycol-N,N,N',N'-tetraacetic acid; N,N-bis(2-hydroxybenzyl)ethylenediamine-N,N-diacetic acid; 1,6-hexamethylenediamine-N,N,N',N'-tetraacetic acid; N-(2-hydroxyethyl)iminodiacetic acid; iminodiacetic acid; 1,2-diaminopropane-N,N,N',N'-tetraacetic acid; nitrilotriacetic acid; nitrilotripropionic acid; the trisodium salt of nitrilotris(methylenephosphoric acid); 7,19,30-trioxa-1,4,10,13,16,22,27,33-octaazabicyclo[11,11,11] pentatriacontane hexahydrobromide; and triethylenetetramine-N,N,N',N'',N''',N'''- hexaacetic acid. It is contemplated that any chelator which binds barium, calcium, cerium, cobalt, copper, iron, magnesium, manganese, nickel, strontium, or zinc will be acceptable for use in the present invention.

In one aspect, the chelators for use in conjunction with the present invention may include ethylenediamine-N,N,N',N'-tetraacetic acid (EDTA); the disodium, trisodium, tetrasodium, dipotassium, tripotassium, dilithium and diammonium salts of EDTA; 1,3-diamino-2-hydroxypropane-N,N,N',N'-tetraacetic acid; 1,3-diaminopropane-N,N,N',N'-tetraacetic acid; O,O'-bis(2-aminoethyl)ethyleneglycol-N,N,N',N'-tetraacetic acid; and 7,19,30-trioxa-1,4,10,13,16,22,27,33-octaazabicyclo[11,11,11] pentatriacontane hexahydrobromide.

In one aspect, the chelators for use in the present invention may include ethylenediamine-N,N,N',N'-tetraacetic acid (EDTA); the disodium salt of EDTA; 1,3-

diaminopropane-N,N,N',N'-tetraacetic acid; and O,O'-bis(2-aminoethyl)ethyleneglycol-N,N,N',N'-tetraacetic acid.

In alternative embodiments the invention provides a preparation (or POEBACA), wherein said chelator in said POEBACA may be selected from the group of chelators consisting of EDTA free acid, EDTA 2Na, EDTA 3Na, EDTA 4Na, EDTA 2K, EDTA 2Li, EDTA 2NH.sub.4, EDTA 3K, Ba(II)-EDTA, Ca(II)-EDTA, Co(II)-EDTA, Cu(II)-EDTA, Dy(III)-EDTA, Eu(III)-EDTA, Fe(III)-EDTA, In(III)-EDTA, La(III)-EDTA, Mg(II)-EDTA, Mn(II)-EDTA, Ni(II)-EDTA, Sm(III)-EDTA, Sr(II)-EDTA, Zn(II)-EDTA, CyDTA, DHEG, DTPA-OH, DTPA, EDDA, EDDP, EDDPO, EDTA-OH, EDTPO, EGTA, HBED, HDTA, HIDA, IDA, Methyl-EDTA, NTA, NTP, NTPO, O-Bistren, and TTHA.

Alternative chelating agents may also be selected from ethylenebis (oxyethylene nitrilio)tetraacetic acid (EGTA) and ethylene diamine tetracetic acid (EDTA), sodium citrate, or oxalate salts such as sodium, potassium, ammonium or lithium oxalate.

Alternative chelating groups include those derived from polyamino-polycarboxylic groups, e.g. those derived from EDTA, DTPA, DOTA, TETA, TETRA, TITRA or 3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (HMPAO) or from such groups substituted, e.g. by a p-isothiocyanato-phenylC.sub.1-3 alkyl, preferably p-isothiocyanatobenzyl. Chelating groups derived from DTPA are also alternative.

In alternative embodiments this invention provides a preparation (or POEBACA), wherein the chelating group is derived from ethylene diaminetetraacetic acid (EDTA), diethylene triamine pentaacetic acid (DTPA), ethylene glycol-0,0'-bis(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), N,N'-bis(hydroxybenzyl)ethylenediamine-N,N'-diacetic acid (HBED), triethylenetetramine hexaacetic acid (TTHA), substituted EDTA or -DTPA 1,4,7,10-tetra-azacyclododecane-N,N',N",N'"-tetraacetic acid (DOTA) and 1,4,8,11-tetraazacyclotetradecane-N,N',N",N'"-tetraacetic acid (TETA), in free form or in pharmaceutically accepted salt form.

In alternative embodiments this invention provides a preparation (or POEBACA), wherein the chelating group is derived from 1,4,7,10-tetraazacyclotridecane-1,4,7,10-tetraacetic acid (TITRA), 1,4,8,11-tetraazacyclotetradecane (TETRA); EDTA, DTPA, DOTA, TETA, TITRA, TETRA or 3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (HMPAO) substituted by p-isothiocyanato-phenyl-C.sub.1-3 alkyl, in free form or in pharmaceutically accepted salt form.

In alternative embodiment this invention provides a preparation (or POEBACA), comprising R/S-gamma-lipoic acid (6,8-dimercaptooctanoic acid) or R/S-alpha-lipoic acid (D,L-thioctic acid).

According to separate but non-limiting embodiments of this invention, "substantially enantiomerically pure" 1,2-dithiolane-3-pentanoic acid (thioctic acid, alpha-lipoic acid) is within the range from at least about 80% pure to at least about 99% pure inclusive as well as every 1% increment within this range (i.e. at least about 80% pure, at least about 81% pure, at least about 82% pure, etc.).

In another embodiment of this invention, D,L-thioctic acid can used in the form of the racemic mixture. According to this invention, a racemic mixture can be comprising two isomers that are found at a ratio within the range from about 20%:80 % to about 80%:20% inclusive as well as every 1% increment within this range (i.e. about 20%:80%, about 21%:79%, about 22%:78%, etc.).

According to another embodiment of this invention, optically active R-(+)-alpha-lipoic acid is used. R-(+)-alpha-lipoic acid is a natural substance that is found in animals and humans, and it acts as coenzyme in the oxidative decarboxylation of .alpha.-keto acids.

Microspheres and liposomes

The invention provides compositions, and methods of using them, wherein ingredients of the composition are encapsulated in a microsphere or a liposome or a combination thereof. Specific, but non-limiting, examples of microspheres according to this invention are provided herein. Specific, but non-limiting, examples of ways of making, administering, and using microspheres or liposomes according to this invention are provided herein. In separate non-limiting embodiments, this invention provides that the micropsheres can be made using lecithin (and/or alternative ingredients as per Table 1 and 2) in amounts in the range from about 0.1 gram to about 40 grams inclusive, including specifically each increment of about 0.1 gram within this range, in a total of 2 ounces of final POEBACA product.

In one embodiment, this invention provides POEBACA comprising gas-filled microspheres. The invention further relates to methods for employing such microspheres as delivery systems to deliver the POEBACAI.

In one embodiment, this invention provides POEBACA comprising at least one member selected from the group consisting of animal and vegetable oils, hydrocarbon oils,

ester oils, silicone oils, higher fatty acids, higher alcohols, sunscreening agents, vitamins, alpha lipoic acid, ferulic acid, and flavors and said solid or semi-solid oil component is at least one member selected from the group consisting of animal and vegetable oils, hydrocarbon oils, ester oils, higher fatty acids, higher alcohols, waxes, sunscreening agents and flavors.

EXAMPLES

Example 1: Amounts of ingredients

Table 2, above, sets forth the amount of ingredients used in exemplary compositions of the invention. Values are normalized to 2 oz or approximately 56 grams

Example 2: Exemplary method for making a microsphere or liposome

	INGREDIENTS:	per 2 fl oz	%
	Lecithin	30.0 gm	50
	EDTA (e.g. Disodium EDTA)	1.0 gm	1.7
	Magnesium Chloride	150.0 mg	0.26
	Alpha Lipoic Acid	100.0 mg	0.17
	Purified Water		37.3
	Ethyl Alcohol		10
	Gum Arabic		0.5

1) Dissolve alpha lipoic acid and EDTA in half the amount of alcohol.

2) Disperse lecithin in half the amount of alcohol and equal amount of water
Heat to 50C, mix with high shear mixing or sonication (sufficient to form microspheres or liposomes) for 20 minutes, cool to 40C.

3) Add magnesium chloride and gum arabic to the remaining amount of water,
Stir for 30 minutes at room temperature

4) Add step number 3 to step number 2. Mix for 20 minutes

5) Add step 4 to step 1, stir gently for 20 minutes.

6) Take a random samples and test for the presence of liposomes.

Example 3: Exemplary method for making a microsphere or liposome

	INGREDIENTS:	per 2 fl oz	%
	Lecithin	30.0 gm	50
	EDTA (e.g. Disodium EDTA)	1.0 gm	1.7
	Magnesium Chloride	150.0 mg	0.26
	Alpha Lipoic Acid	100.0 mg	0.17
	Purified Water		37.3
	Ethyl Alcohol		10
	Gum Arabic		0.5

1) Dissolve alpha lipoic acid in half the amount of alcohol.

2) Disperse lecithin in half the amount of alcohol and equal amount of water

Heat to 50C, mix with high shear mixing or sonication (sufficient to form micropsheres or liposomes) for 20 minutes, cool to 40C.

3) Add EDTA, magnesium chloride and gum arabic to the remaining amount of water, Stir for 30 minutes at room temperature

4) Add step number 3 to step number 2. Mix for 20 minutes

5) Add step 4 to step 1, stir gently for 20 minutes.

6) Take a random samples and test for the presence of liposomes.

Example 4: Amounts of ingredients

Table 4, above, sets forth the amount of ingredients used in exemplary compositions of the invention. Values are normalized to a "00" capsule, containing approximately 800 mg total (typically in the range of approximately 700 – 900 mg)

Example 5: Exemplary method for making an exemplary breast and prostate health supplement of the invention

	INGREDIENTS:	per about 760 mg	%
	Di-indolemethane	100 mg	13.15
	Grape (skin) extract	200 mg	26.3
	Calcium D-Glucarate	200 mg	26.3
	Medium chain triglycerides (MCTs)	50 mg	6.58
	Lecithin (Phosphatidyl choline 20-30%)	50 mg	6.58

OTHER INGREDIENTS:

Cellulose powder(13.52%), magnesium silicate (5.65%), magnesium stearate (0.52%), silicon dioxide(1.34%)

CAPSULE SIZE: "00" Vcaps
CAPSULE FILL: 760 mg

PREPARATION:

1. Sift calcium-D-glucarate into a planetary mixer (e.g. Hobart) or v-blender tumbler through # 18 mesh screen.
2. Sift grape extract or grape skin extract or wine extract, e.g. red wine extract, into a planetary mixer (e.g. Hobart) or v-blender tumbler through # 18 mesh screen. Mix for 8+ minutes
3. Sift DIM into a planetary mixer (e.g. Hobart) or v-blender tumbler through # 18 mesh screen. Mix for 8+ minutes
4. Sift MCTs, magnesium silicate and lecithin into a planetary mixer (e.g. Hobart) or v-blender tumbler through # 18 mesh screen. Mix for 8+ minutes
5. Sift Cellulose powder into a planetary mixer (e.g. Hobart) or v-blender tumbler through # 18 mesh screen. Mix for 8+ minutes
6. Sift magnesium stearate and silicone dioxide through # 40 mesh screen into the mixer, mix for 4+ minutes.

Example 6: Combination kits (as exemplified by a kit comprising Prep A and Prep B).

A detoxification preparation, Prep A, is made. Prep A is a fluid, and it contains per 2 fluid ounces:

Ingredients (Prep A)	Amount (per 2 oz.)
Lecithin	30.0 gm
EDTA (e.g. Disodium EDTA)	1.0 gm
Magnesium Chloride	150.0 mg
Alpha Lipoic Acid	100.0 mg
Purified Water	
Ethyl Alcohol	
Gum Arabic	

A breast health preparation is made, Prep B, is made. Prep B is in the form size "00" vegetable capsules (Vcap or v-cap), and it contains per capsule:

Ingredients (Prep B)	Amount (per "00" Vcap)
Di-indolemethane	80-120 mg
Grape (skin) extract	150-250 mg
Calcium D-Glucarate	150-250 mg
Medium chain triglycerides (MCTs)	25-100 mg
Lecithin (Phosphatidyl choline 20-30%)	25-100 mg
Lycopenes and carotenoids (optional)	10-150 mg

This invention provides kits or a combinations of preparations comprising: i) a first preparation that contains ingredients selected from the Groups A-G as exemplified in Table 1 and in the amounts as exemplified in Table 2; and ii) a second preparation containing ingredients selected from Groups 1-5 as exemplified in Table 3 and in the amounts as exemplified in Table 4.

Examples 4 and 6 provide non limiting exemplifications of such a kit, e.g., where the two exemplary preparations in the kit are Prep A and Prep B. This invention also provides modifications and alterations of the provided Examples, specifically according the different embodiments of preparations provided herein. For example the amount of each ingredient in a particular preparation can be altered and modified in specific embodiments, and these amounts include those amounts listed in Table 2 (including in the last column of Table 2), and those amounts listed in Table 4 (including in the last column of Table 4).

This invention also provides methods for using such a kit, as is exemplified in Examples 4 and 5, e.g., that comprise: i) a first preparation that contains ingredients selected from the Groups A-G as exemplified in Table 1 and in the amounts as exemplified in Table 2; and ii) a second preparation containing ingredients selected from Groups 1-5 as exemplified in Table 3 and in the amounts as exemplified in Table 4.

Example 7. Methods of using combination kits.

In this non-limiting example Prep B (e.g. for breast or prostate tissue health) is taken orally as follows.

a) On Day 1, the consumer, e.g. human or animal (e.g. a pet or livestock) starts taking Prep B; the suggested amount for a typical 75 kg adult is: two size "00" capsules per day, (e.g. one with breakfast and one with dinner). This regimen is maintained daily

for weeks or months or years. In one aspect, Prep B is incorporated into the regular diet, and it is taken daily, e.g. for years.

b) On day 31, after the consumer has been taking Prep B daily for about one month, start also taking Prep A (for detoxification) orally; the suggested amount is: 2-4 ounces per week (e.g. for a regimen lasting 5-20 weeks (e.g. depending on the systemic levels of toxins or heavy metals), e.g. at night, and at least one or two hours after the last meal of the day. Prep A can be taken one time a week (e.g. 1 or 2 oz. each time) or two times a week (1 or 2 oz. each time).

c) Prep A can be discontinued after the 10-20 week regimen is completed. If necessary (depending on the systemic level of toxins or heavy metals) it may be useful to repeat another 10-20 week regimen of Prep A.

This combined method of use and variations thereof are intended for protection according to this invention; and variations can be, e.g. with respect to the amount of each ingredient (according to embodiments provided herein, and as exemplified in Table 2 and in Table 4.

This invention also provides that Prep A can be taken independently of Prep B, e.g. as illustrated in Example 7, but without Prep B.

Likewise, this invention also provides that Prep B can be taken independently of Prep A, e.g. as illustrated in Example 7, but without Prep A.

This combined method of use and variations thereof are intended for protection according to this invention; and variations can be with respect to the amount of each ingredient (according to embodiments provided herein, and as exemplified in Table 2 and in Table 4.

It is intended that all the separate embodiments and aspects provided herein according to this invention (including, in non-limiting fashion, products and methods) may be further be modified (resulting in additional patent claims intended for protection) by the addition of water-soluble vitamins and/or by the addition of fat-soluble vitamins (for the purpose of patent protection). Thus, this invention intends to reserve protection for all the embodiments and aspects described herein, such as products that contain (or methods that use) any ingredients from any of Groups A, B, C, D, E, F, 1, 2, 3, 4, and/or 5, with further modifications (or claim limitations) through the addition of anywhere from one to 100 vitamins as exemplified in Table 5 (specifically Groups 6 and 7), and in the amounts as illustrated in Table 6; the result is additional embodiments and aspects

intended for patent protection (as patent claims containing limitations regarding ingredient quantities and/or quantity ranges).

The examples in Table 5 are non-limiting examples of molecular forms as provided herein. It is provided that it is the intent of this invention to specifically include not only the specific examples listed in Table 5, but also derivatives, precursors, and active metabolites of the vitamins listed in Table 5, as these are known in the art, and this invention seeks patent protection for embodiments and aspects provided herein (e.g. products and methods) that include these derivatives, precursors, and active metabolites (many forms of these molecules are found in references such as http://ods.od.nih.gov, http://www.chiro.org/nutrition, www.truestarhealth.com/Notes/2461007.html, www.vitamins-nutrition.org, and www.anyvitamins.com, www.supplementwatch.com, the information from these websites is hereby incorporated herein by reference in its entirety). As a non-limiting example, beta-carotene is a precursor to vitamin A, and it is thus provided according to this invention. There is some inconsistency in the literature with respect to the spelling and classification of certain vitamins. Thiamine is sometimes spelled thiamin. Cobalamin is sometimes spelled cobalamine. Folates are classified as vitamin B9, but sometimes as vitamin B8.

Table 5 Ingredients used in the compositions and methods of the invention.

(See Table 6 for alternative amounts according to this invention)

Group	Group Members (Non-limiting examples are listed for each group)

Group	Group Members (Non-limiting examples are listed for each group)
6	Water soluble vitamins, such as vitamin C and the B vitamins (e.g. folic acid and folinic acid) Vitamin C including ascorbic acid and ascorbates, such as calcium ascorbate, chromium ascorbate, magnesium ascorbate, manganese ascorbate, molybdenum ascorbate, sodium ascorbate, zinc ascorbate, l-ascorbic acid, l-(+)-ascorbic acid, l,3-ketothreohexuronic acid; also including metabolites such as dehydroascorbate (oxidized ascorbic acid), calcium threonate, xylonate and lyxonate; also including precursors and derivatives such as ascorbyl palmitate (a vitamin C ester, likely to hydrolyzed to ascorbic acid and palmitic acid). B-Vitamins including B1 (thiamine), B2 (riboflavin), B3 (niacin, niacinamide, inositol hexaniacinate, nicotinamide, nicotinic acid), B5 (pantothenates, such as pantothenic acid, calcium pantothenate, pantethine), B6 (pyridoxine, PLP, Pyridoxal-5'-Phosphate), B7 (biotin), B9 (folinic acid, folic acid, folates such as methylfolate, or 5-formyl tetrahydrofolate), and B12 (cobalamin and derivatives such as, hydroxycobalamin, methylcobalamin, adenosylcobalamin, cyanocobalamin, hydroxycyanocobalamin). Products containing variations of these vitamins are also included herein (for patent protection) and include, e.g. folinic acid (e.g. as calcium folinate).

Group	Group Members (Non-limiting examples are listed for each group)
7	Fat soluble vitamins such as vitamins A, D, E, and K Vitamin A (including retinol and retinol derivatives such as retinoic acid) and carotenoids (which includes over 600 members such as lycopene and lutein). Vitamin D including 1,25-dihydroxyvitamin D, calciferol, calcipotriol, cholecalciferol, ergocalciferol (vitamin D2), irradiated ergocalciferol Vitamin E including alpha tocopherol, tocopherol, tocopheryl acetate, tocopheryl succinate. Vitamin K including forms such as phylloquinones, menaquinones, menadione, and menatetrenone (vitamin K2).

Table 6. Amounts of ingredients used in the compositions and methods of the invention.

Vitamin	Exemplary amounts*	Alternative amounts* intended for protection as claimed according to this invention (both individually and collectively as a group).
C (ascorbic acid)	500 mg	From about 0.01 mg to about 10 grams inclusive, including specifically each increment of about 0.01 mg within this range.
B1 (thiamine),	2 mg	From about 0.01 mg to about 500 mg inclusive, including specifically each increment of about 0.01 mg within this range.
B2 (riboflavin)	2 mg	From about 0.01 mg to about 500 mg inclusive, including specifically each increment of about 0.01 mg within this range.
B3 (niacin, niacinamide)	20 mg	From about 0.01 mg to about 500 mg inclusive, including specifically each increment of about 0.01 mg within this range.
B5 (pantothenates, such as pantothenic acid)	10 mg	From about 0.01 mg to about 500 mg inclusive, including specifically each increment of about 0.01 mg within this range.
B6 (pyridoxine)	2 mg	From about 0.01 mg to about 500 mg inclusive, including specifically each increment of about 0.01 mg within this range.
B7 (biotin)	0.5 mg	From about 0.01 mg to about 50 mg inclusive, including specifically each increment of about 0.01 mg within this range.
B9 (folic acid and folates)	0.5 mg	From about 0.01 mg to about 50 mg inclusive, including specifically each increment of about 0.01 mg within this range.
B12 (cobalamin and derivatives).	5 mcg	From about 0.01 mcg to about 1 mg inclusive, including specifically each increment of about 0.01 mcg within this range.
A	1 mg	From about 0.01 mg to about 500 mg inclusive, including specifically each increment of about 0.01 mg within this range.
D	10 mcg	From about 0.01 mg to about 1 mg inclusive, including specifically each increment of about 0.01 mg within this range.
E	10mg	From about 0.01 mg to about 500 mg inclusive, including specifically each increment of about 0.01 mg within this range.
K	0.1 mg	From about 0.01 mg to about 50 mg inclusive, including specifically each increment of about 0.01 mg within this range.

*Note: Amounts are in reference to a daily dose, the form of which may be, e.g., a powder, a liquid, a pill (including a capsule, a tablet), a "power bar", & /or a candy (including candy bars, hard candies, "gummy" candies, and gum balls).

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Example 8 Breast and prostate health supplement

	INGREDIENTS:	per about 660 mg
	Di-indolemethane	100 mg
	Grape (skin) extract	200 mg
	Calcium D-Glucarate	200 mg
	Medium chain triglycerides (MCTs)	45 mg
	Lecithin (Phosphatidyl choline 20-30%)	45 mg
	Folic Acid	0.5 mg
	Folinic Acid (as Calcium Folinate)	0.5 mg
	Lycopenes and/or carotenoids (optional)	10-50 mg

OTHER INGREDIENTS:

Cellulose powder, magnesium silicate, magnesium stearate.

CAPSULE SIZE: "00" Vcaps

CAPSULE FILL: 660 to 740 mg

PREPARATION:

1. Sift calcium-D-glucarate into a planetary mixer (e.g. Hobart) or v-blender tumbler through # 18 mesh screen.

2. Sift Grape extract or grape skin extract or wine extract, e.g. red wine extract, into a planetary mixer (e.g. Hobart) or v-blender tumbler through # 18 mesh screen. Mix for 8+ minutes

3. Sift DIM into a planetary mixer (e.g. Hobart) or v-blender tumbler through # 18 mesh screen. Mix for 8+ minutes. Optionally, sift lycopenes and or carotenoids into a planetary mixer (e.g. Hobart) or v-blender tumbler through # 18 mesh screen. Mix for 8+ minutes.

4. Sift MCTs, magnesium silicate and lecithin into a planetary mixer (e.g. Hobart) or v-blender tumbler through # 18 mesh screen. Mix for 8+ minutes

5. Sift Cellulose powder into a planetary mixer (e.g. Hobart) or v-blender tumbler through # 18 mesh screen. Mix for 8+ minutes

6. Sift magnesium stearate and silicone dioxide through # 40 mesh screen into the mixer, mix for 4+ minutes.

7. Encapsulate "00" @ 640 mg.

8. Evaluate: Disintegration time, weight variation, content uniformity.

The benefits of using the preparations provided herein are many and can be additive or synergistic in regards to individual ingredients in a preparation comprising a plurality of ingredients. For example, it has been reported that indole-3-carbinol (I3C) and its dimer 3,3'-diindolylmethane (DIM), obtained from dietary consumption of cruciferous vegetables, have multiple biochemical activities. Both compounds have been reported to be clinically effective in treating precancerous lesions of the cervix and laryngeal papillomas, pathologies with a human papillomavirus (HPV).

Various modifications of the invention in addition to those shown and described herein will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

In alternative embodiments this invention provides a preparation (or POEBACA), comprising ocular drug delivery vehicle of an oil-in-water submicron emulsion consisting essentially of about 0.5 to 50% of a first component of an oil, about 0.1 to 10% of a second component of an emulsifier, comprising a phospholipid, about 0.05 to 5% of a non-ionic surfactant and an aqueous component, said submicron emulsion having a mean droplet size in the range of 0.05 to 0.5 μm, and a weight ratio of surfactant to oil of about 1:1 or less.

In alternative embodiments this invention provides a method for transferring ingredients making up a preparation of encapsulated bioavailable chelating agents (i.e. POEBACAI) across a cellular membrane by encapsulating said ingredients within liposomes and carrying said POEBACAI to the cellular membrane where the liposomes will be taken up by the cells, thereby transferring the POEBACAI across the cellular membrane. POEBACAI can be introduced into the interior of a cell of a living organism wherein the liposomes will be decomposed, releasing the POEBACAI to the interior of the cell. The released POEBACAI will complex intracellularly deposited toxic heavy metals, permitting the more soluble metal complex to transfer across the cellular membrane from the cell and subsequently be removed from the living organism.

In alternative embodiments this invention provides a method of transferring POEBACAI across a cellular membrane comprising: encapsulating said POEBACAI within liposomes; and carrying said liposome encapsulated POEBACAI to said cellular membrane, whereby said liposome encapsulated POEBACAI will transfer across said cellular membrane.

In alternative embodiments this invention provides a method of introducing a POEBACAI into the interior of a cell in accordance with the method of claim 1 wherein said cellular membrane is the membrane wall of said cell and said encapsulated POEBACAI passes through the membrane wall of said cell into the interior of said cell, wherein said liposomes will be decomposed, thereby releasing said POEBACAI to the interior of said cell.

In alternative aspects this invention provides a method wherein said cell is a cell of a living organism and said POEBACAI is carried to said cell by injecting a saline suspension of said liposome POEBACAI into the blood stream of said living organism whereby said POEBACAI is carried to the cell within the blood

In alternative embodiments this invention provides a method for the removal of intracellularly deposited toxic heavy metals comprising:

encapsulating a POEBACAI agent within liposomes;

introducing said liposomal POEBACAI into the blood system by one or more of the following routes: oral administration, intravenous injection or infusion, by topical lotion, spray or cream, or transdermal patch; whereby

said liposome POEBACAI is carried to said body cells within said blood system;

said liposome POEBACAI is passed through the cell wall into the interior of said body cell;

said POEBACAI is released to the interior of said cell by the biological degradation of said liposome by lysosomal enzymes, said released POEBACAI complexing said intracellularly deposited toxic metal;

said complexed toxic metal is passed through the cell wall into said blood stream; and

said complexed toxic metal is removed from said blood stream and the body by normal body processes.

In alternative embodiments this invention provides a preparation or POEBACA wherein said liposomes are prepared from a mixture of lecithin and cholesterol.

In alternative embodiments this invention provides a POEBACAI comprising a member chosen from the group consisting of EDTA, EGTA, and DTPA.

In alternative embodiments this invention provides a detoxification method wherein said toxic heavy metals are selected from the group consisting of plutonium, gold, mercury, and lead, beryllium, and cadmium.

Any gel can be used in the practice of the present invention. The materials which can be used to form such gels include but are not limited to: carbohydrates such as cellulosics, methylcellulose, starch and modified starch, agarose, gum arabic, ghatti, karay, tragacanth, guar, locust bean gum, tamarind, carageenan, alginate, xanthan, chickle, collagen, polyacrylamide, polysiloxanes (polyanhydrides, e.g., malic anhydride copolymers, polyacrylates, e.g., hydroxyethylpolymethycrylate polymethylmethacrylate, polyethylethacrylate polymethacrylate, ethylenevinylacetate copolymers, ethylenevinylalcohol copolymers, polyorthoesters, .epsilon.-caprolactones, amino acid polymers such as gelled albumin, amino acid polymers and copolymers and gelatins, and other organic or inorganic polymers which can be mixed with liposomes in vitro.

After the mixture forms a gel the resulting liposome-gel matrix can be implanted in tissues. In a particularly useful embodiment of the present invention soft gel matrices such as agarose, collagen and the like containing sequestered liposomes may be injected in vivo. Alternatively, gels such as methylcellulose can be formed in the tissues after inoculation of liposomes in a suspension containing the gel material. After inoculation the suspension forms a gel and the liposomes remain sequestered in the gel matrix rather than dispersed and cleared. Regardless of the method used for preparing and implanting the gel matrix, the release of a liposome entrapped bioactive chelating agent or other POEBACAI is prolonged and the relative concentration of the agent at the site of inoculation is increased.

Virtually any POEBACAI (including chelating agents) as well as virtually any other bioactive agent can be entrapped within the liposomes for use according to the present invention. Such agents include but are not limited to antibacterial compounds, antiviral compounds, antifungal compounds, anti-parasitic compounds, tumoricidal compounds, proteins, toxins, vitamins, trace minerals, heavy metals, enzymes, hormones, neurotransmitters, lipoproteins, glycoproteins, immunoglobulins, immunomodulators, dyes, radiolabels, radio-opaque compounds, fluorescent compounds, polysaccharides, cell receptor binding molecules, anti-inflammatories, antiglaucomic agents, mydriatic compounds, anesthetics, nucleic acids, polynucleotides, etc.

In fact, if concurrent therapy is desired, two or more POEBACAI (including chelating agents) or other bioactive agents may be entrapped in one liposome population which is sequestered in the gel matrix. Alternatively, two or more liposome populations (of the same or different types of liposomes, e.g. mixtures of SPLVs, MPVs, SUVs,

LUVs, REVs, etc.) which each entrap the same or different POEBACAI (including chelating agents) or other bioactive chelating agents may be sequestered in the gel matrix.

In yet another embodiment of the present invention the gel can be used as a vehicle for the same or different bioactive chelating agents and other POEBACAI than those entrapped by liposomes.

In certain therapeutic applications it may be desired to deliver a relatively high dose of a drug compound (i.e., compound A) followed by a sustained dose of the same or another compound (i.e., compound B). According to the present invention, this is readily accomplished by entrapping compound B in liposomes, sequestering the liposomes in a gel matrix containing compound A, and administering the same in vivo in a single inoculation. Thus, rapid delivery of compound A by diffusion from the gel, and slow sustained delivery of compound B by release from the liposomes is effected.

The release of the bioactive chelating agents may be controlled by the type of liposomes used and the membrane composition of the liposome bilayers as well as by the type and porosity of the gels used. The rate of release is also dependent upon the size and composition of the bioactive chelating agent itself. The liposome itself is the first rate limiting factor in the release of entrapped bioactive chelating agents. The rate of release may depend upon the number of bilayers, the size of the liposomes and most importantly the bilayer composition.

In one aspect, "stabilizers" such as sterols, cholesterols and the like can be added to the phospholipid bilayers in order to alter the permeability of the liposome, e.g., as described by Papahadjopoulos, D., Kimilberg, H. K., 1974, in Progress in Surface Science, ed. S. G. Davison, pp. 141-232, Oxford: Pergamon; Demel, R. A., Bruckdorf, K. R., Van Deenan, L. L., 1972, Biochem. Biophys. Acta, 255:331-347.

In one aspect, it is important that the stable liposomes will release their contents upon contact with body fluids or culture media. The rate of release may be controlled by modifying liposome membranes accordingly using known methods.

Use of the Liposome-Gel Preparation in Living Systems.

The liposome-gel compositions of the present invention may be used for sustained delivery of a bioactive chelating agent to cells and/or fluids in vivo and in vitro. When used in vivo, the liposome-gel compositions of the present invention may be administered before or after gel formation. Routes of administration include but are not limited to: inoculation, injection or infusion, (e.g., intraperitoneal, intramuscular, subcutaneous,

intra-aural, intra-articular, intra-mammary, etc.), topical application (e.g., on areas, such as eyes, ears, skin, mucous membranes, or on afflictions such as wounds, burns, etc.), and by absorption through epithelial or mucocutaneous linings (e.g., nasal, oral, vaginal and other epithelial linings, gastrointestinal mucosa, and the like).

For example the liposome-gel preparations of the present invention may be inoculated or infused *in vivo* to provide for the sustained systemic release of the bioactive chelating agent. Such applications may be particularly useful for the systemic release of drugs such as hormones (e.g., to control growth, fertility, sugar metabolism, etc.) or antimicrobials to control and treat infections, etc.

In an alternative example, the liposome-gel preparation may be applied topically. Topical application may be particularly useful for the treatment of wounds (either surgical or non-surgical wounds) where the sustained release of POEBACAI (including chelating agents), antimicrobials and/or blood clotting factors may be helpful in the healing process. Similarly, the liposome-gel preparation may be topically applied to burns for the sustained release of POEBACAI (including chelating agents), antimicrobials and/or cell growth factors. The liposome-gel preparation may also be applied in the ear to treat infections by providing sustained release of POEBACAI (including chelating agents), antimicrobials; this would reduce the necessity of repeated applications of the bioactive chelating agent in the form of ear drops.

In another alternative embodiment, a liposome-gel preparation may be administered orally for sustained release. Such application may be useful for sustained release to oral epithelium and other oral tissues and for sustained release to epithelia of the alimentary tract.

The liposome-gel preparations of the present invention may also be used in vitro to provide for sustained release of a POEBACAI (including chelating agents) into the cell or tissue culture medium. Such POEBACAI (including chelating agents) may also include but are not limited to nutrients, drugs, hormones, growth factors, etc. The liposome-gel preparation may be used as a support for cell adhesion and growth; for instance, a liposome-collagen gel may be especially useful for culturing muscle cells, nerve cell, or liver cells. When the liposome-gel preparation is applied as an overlay, a liposome-agarose gel may be particularly useful.

Many methods for making preparations comprising the ingredients provided herein as well as methods for making preparations comprising micropsheres or liposomes

are many in the art. For particularly useful references regarding these methods, see the references listed below, which are hereby incorporated by reference in their entirety.

The following US patents are hereby incorporated by reference herein in their entirety: 5,990,1535,000,887; 4,994,213; 4,981,692; 4,975,282; 4,963,297; 4,952,405; 4,944,948; 4,927,637; 4,927,571; 4,923,854; 4,906,476; 4,897,384; 4,895,719; 4,891,208; 4,885,172; 4,880,635; 4,873,088; 4,861,580; 4,839,175; 4,837,028; 4,828,837; 4,822,777; 4,818,537; 4,804,539; 4,781,871; 4,766,046; 4,762,915; 4,752,425; 4,737,323; 4,721,612; 4,714,571; 4,708,861; 4,698,299; 4,668,638; 4,666,831; 4,610,868; 4,588,578; 4,564,599; 4,522,803; 4,483,929; 3,932,657; 3,909,284; and 3,576,663.

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